Library of Modulator of Protein-protein Interactions (PPI)

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ChemDiv, Inc.

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PPI BIASED CHEMISTRY

(Yin & Yang Algorithm – Balance of Efficiency and Innovation)

Design of PPI Library Principles:

- ❖Diversity
- ❖3D-Shape
- ❖Escape from flatland
- ❖Drug-likeness
- ❖Natural product likeness
- ❖Targeted Diversity

Between 40,000 and 200,000 protein-protein interactions have been predicted to exist within the human interactome

Protein-protein interactions (PPIs) play a key role in nearly every biological function and are a promising new class of biological targets for therapeutic intervention

Main problem - PPIs include the most poorly druggable targets

Diversity of PPI Library

❖Nature “sees” molecules as 3D surfaces of chemical information. Therefore the biological activity of any given molecule is intrinsically dependent upon its 3D shape

❖The molecular shape diversity of a small molecule library is the most fundamental indicator of overall functional diversity

❖Although the term “diversity” is somewhat subjective, there are six principle components of structural diversity that have been consistently identified in the literature

1) Scaffold diversity - presence of a range of distinct molecular scaffolds;
2) Functional group diversity - variation in the functional groups present;
3) Appendage diversity (substituent or building-block diversity) - variation in structural moieties around a common scaffold;
4) Stereochemical diversity - variation in the orientation of potential macromolecule-interacting elements;
5) Conformational diversity - variation of possible conformers of molecules;
6) Chain diversity – presence of different distinct chains (especially if scaffold is not determined uniquely)

“Escape from Flatland” – New Approach for Scaffold & Library Design

Inspired by: Frank Lovering, et.al. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. J. Med. Chem. 2009, 52, 6752–6756

Fsp3 = number of sp3-hybridized carbons/ total carbon count

- **The increase of scaffold/molecule saturation leads to:**
  - **More diverse set of compounds**
  - **More highly complex molecules**
  - **Natural product-likeness**
  - **Access to greater chemical space**
- **Better complement to the spatial subtleties of target proteins**
- **3D-dimensionality may result in greater selectivity**
- **Higher water solubility**
- **Better phys-chemical parameters (logP and PSA)**
- **Very low increase of MW**
- **New stereo-centers**
- **As result: Faster transition of compound from discovery to drugs**

One difficulty: more complex scaffold/molecules require new perfect synthetic approaches.
Diversity oriented synthesis!!!

Fsp3 of Small Molecules in Clinical Trials

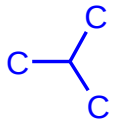
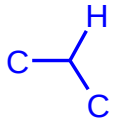
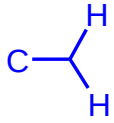
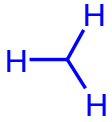
Phase	#compounds	Fsp3%
Launched	1719	45.4
Phase 2&3	2315	42.7
Discontinued& Withdrawn	2146	42.4
Phase 1	1223	41.1
Preclinical	21204	37.7

(compounds with MW>650 were excluded)

Fsp3 is important drug-like parameter

Comparison of Drug-like vs Natural Libraries 1

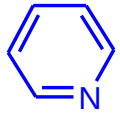
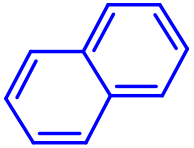
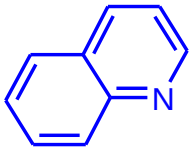
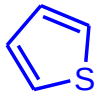
Content of sp3 carbons (frequency of occurrence)

Type of sp3 carbons	Content in Kinase Targeted library	Content in Natural Product library
	**23.2%**	**68.1%**
	**59.8%**	**92.3%**
	**87.5%**	**95.6%**
	**69.3%**	**87.8%**

Drug-like library – Kinase database (Integrity) ~25K compounds
Natural Product library – combined sources ~ 25K compounds
(compounds with MW>650 were excluded)

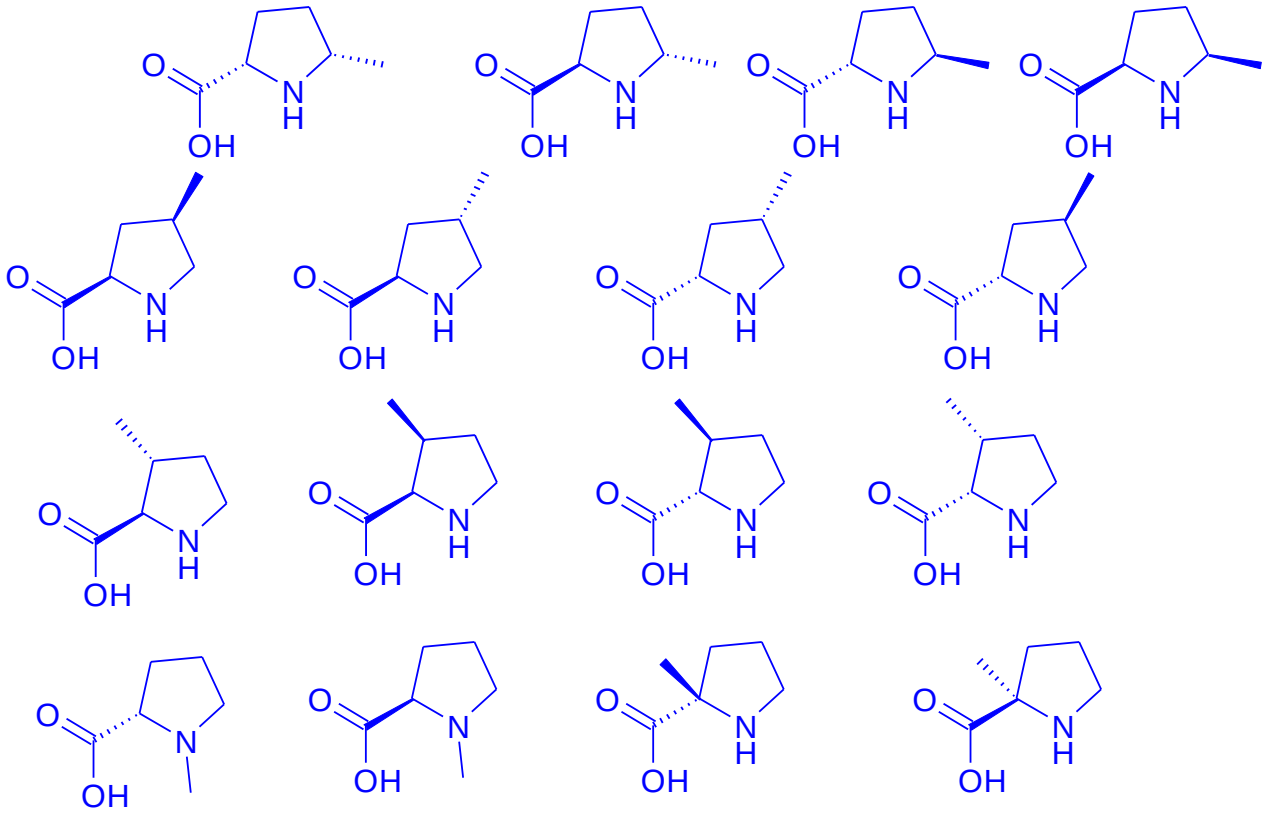
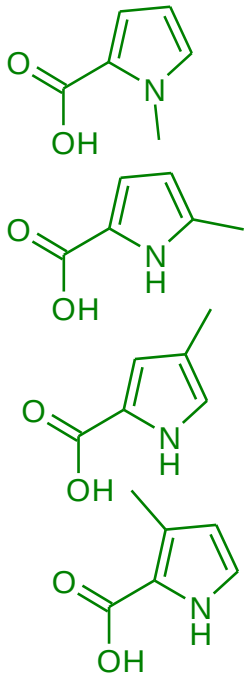
Comparison of Drug-like vs Natural Libraries 2

Content of flat fragments (frequency of occurrence)

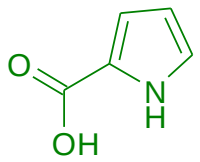
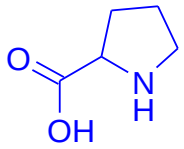
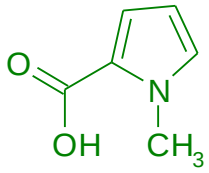
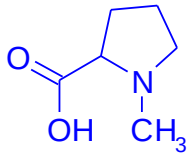
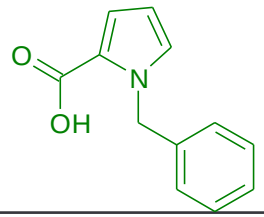
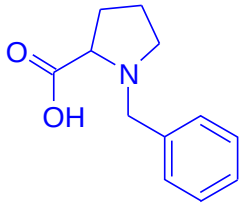
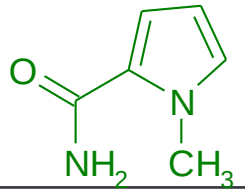
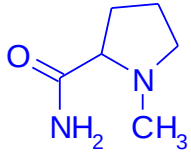
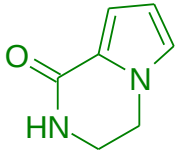
Type of flat fragment	Content in Kinase Targeted library	Content in Natural Product library
	91.9%	59.7%
	34.8%	7.80%
	2.03%	2.53%
	4.48%	2.51%
	5.09%	1.04%

Drug-like library – Kinase database (Integrity) ~25K compounds
Natural Product library – combined sources ~ 25K compounds
(compounds with MW>650 were excluded)

Increased 3D-Diversity of Flexible vs Flat Structures Example: Proline-like compounds

16 Isomers of Methyl-proline	4 Isomers of flat analogs
	

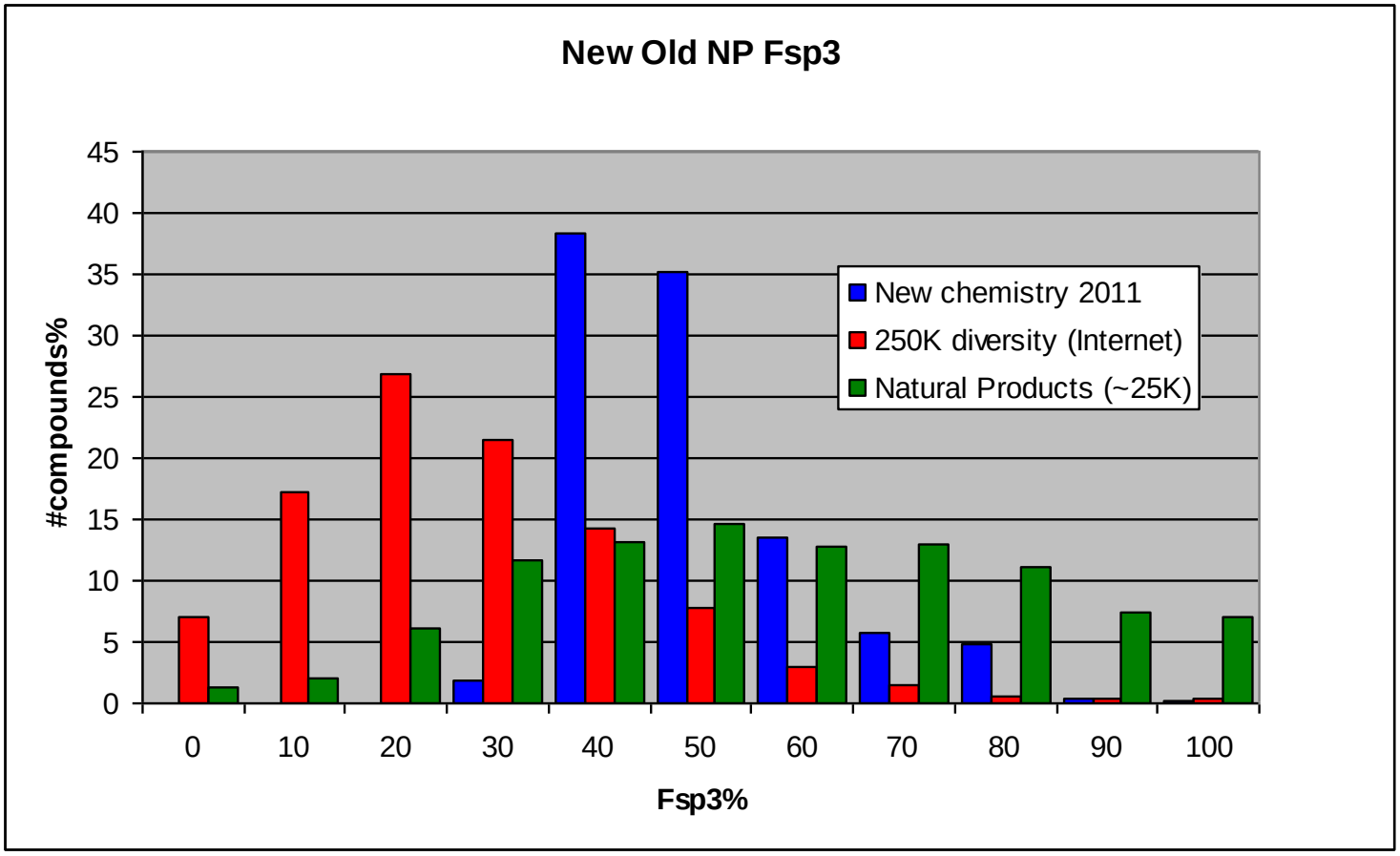
Proline-like compounds 2

Structure Flat compounds	Phys-chemical properties	Structure Flexible	Phys-chemical properties
	Fsp^3=0.0000 logP=0.980 logSW=-3.44 PSA=53.09		Fsp^3=0.8000 logP=-2.330 logSW=-0.890 PSA=49.33
	Fsp^3=0.167 logP=1.180 logSW=-2.25 PSA=42.23		Fsp^3=0.833 logP=-0.840 logSW=-0.826 PSA=40.54
	Fsp^3=0.083 logP=2.81 logSW=-4.17 PSA=42.23		Fsp^3=0.417 logP=1.540 logSW=-1.445 PSA=40.54
	Fsp^3=0.167 logP=0.680 logSW=-2.15 PSA=48.02		Fsp^3=0.833 logP=-1.00 logSW=-0.784 PSA=46.33
	Fsp^3=0.286 logP=1.13 logSW=-3.71 PSA=34.03		Fsp^3=0.857 logP=0.100 logSW=-0.454 PSA=32.34

Flexibility improves phys-chemical properties (logSW, ClogP, PSA) of scaffolds or building blocks

Parameter	Scaffold	Molecule
No undesirable functionalities (MedChem filters)		
No undesirable chemotypes (MedChem filters)		
Amide bonds	No more 2 amide bonds (cyclic or linear)	No more 2 amide bonds (cyclic or linear)
Aromatic rings	No more 2 aromatic rings	No more 3 aromatic rings
MW	100<MW<350	150<MW<500
Fsp3 Sp3-Ring C atom	>0.30 >0	>0.30 >1
ClogP	-1.0 <ClogP< 3.5	0 <ClogP<5.0
PSA	10<PSA<60	40<PSA<90
HBA/HBD	<6/2	<8/3
Rotatable bonds	<6	<8

Comparison of Newest Chemdiv's Library (~20K), Available Diversity Set (Internet, 250K) and Natural Products (~25K)



Quo vadis?

Our chemistry is becoming more similar to natural products!

STRUCTURE of PPI BIASED LIBRARY

❖Library consists of several complementary parts:

❖Nonpeptide Peptidomimetics (based on the PPI biased substructures) ~25K
❖Set of Recognition Elements (gamma-, beta-turns, dipeptide mimetics) ~30K
❖Tripeptide mimetics ~(3K – upon request)
❖Shape (helix, beta-sheet, strand, loop) mimetics ~10K
❖3D-mimetics (single Isomers, caged compounds, etc.) ~3K
❖Set of Spiro-compounds ~5.5K
❖Set of Eccentric compounds ~7K
❖Set of cyclic Ugi-compounds ~40K
❖Set "Beyond Flatland" ~30K

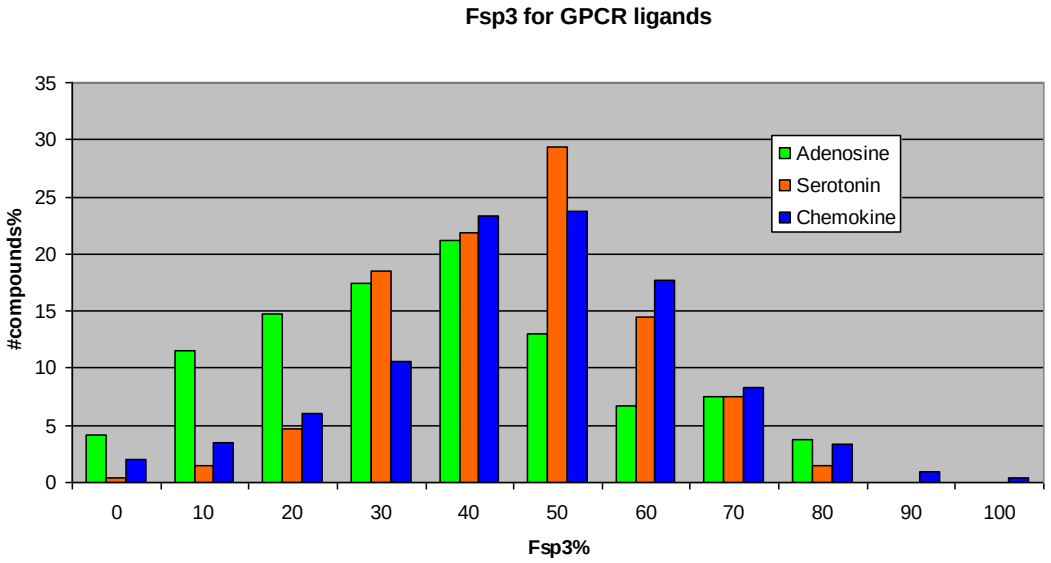
❖PPI Focused sub-libraries:
❖PDZ-domain inhibitors ~ 5K
❖MDM2 binding inhibitors ~8K
❖CD16a binding inhibitors ~2K

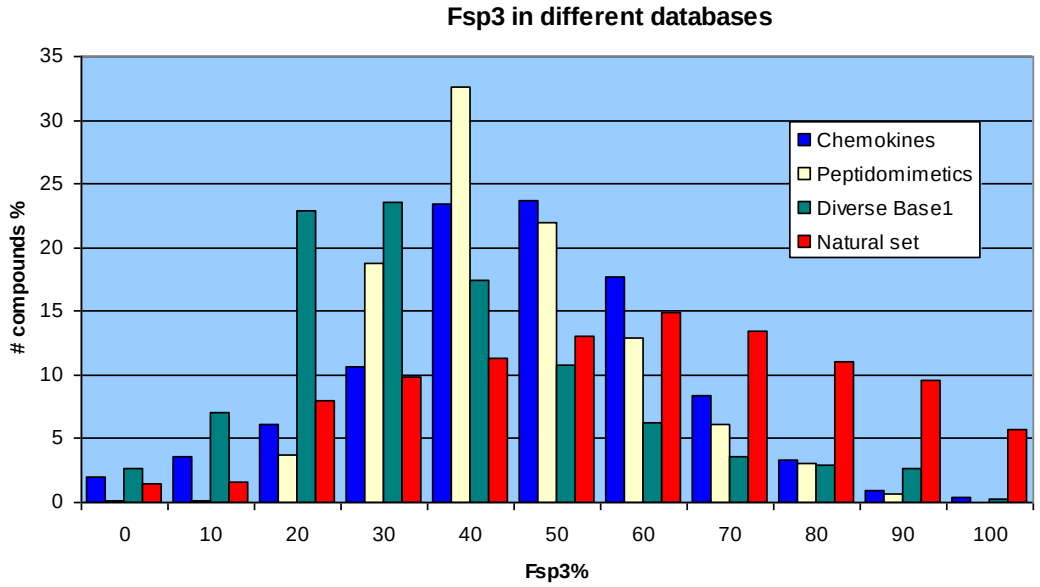
❖pGPCRs Focused sub-libraries:
❖Chemokines ~10K
❖Hedgehog pathway ~10K
❖Neurotensin ~2K
❖etc.

PPI biased library contains about 100K compounds (overlapping allowed)

Nonpeptide Peptidomimetics

Fsp3 Difference of Different GPCR Ligands and Libraries





Virtual database from Integrity & MedChem sources:

- ❖**Chemokine - 4.2K ligands**
- ❖**Serotonin - 8.6K ligands**
- ❖**Adenosine - 2.4K ligands**
- ❖**Natural set - 25K compounds**

Available collection of compounds:

- ❖**Peptidomimetic Library ~ 20K compounds**
- ❖**Diverse set - 250K compounds**

Chemokines Set and Peptidomimetic Library have a similar distribution of the Fsp3 Chemokines are very different from diverse and natural sets

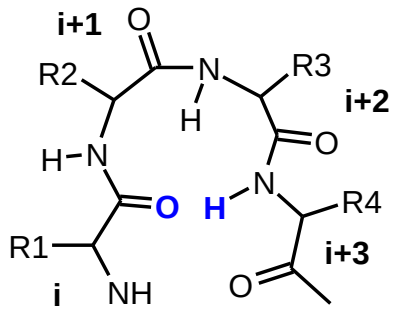
Set of Recognition Elements (gamma-, beta-turns, dipeptide mimetics)

❖Turns are defined as regions where a peptide chain reverses its overall direction

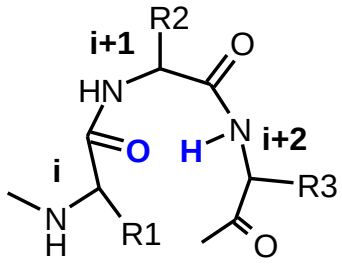
❖Gamma-turns involve three residues and a hydrogen bond is often formed between residues *i* and *i* + 2 so that a pseudo-7-membered ring is formed

❖Chain reversal in beta-turns involves four residues and a hydrogen bond may then be formed between residues *i* and *i* + 3 so that forms a pseudo-10-membered ring

❖A common method to mimic the bioactive conformation of peptides is to synthesize conformationally constrained analogues via backbone-backbone or backbone-side chain cyclization



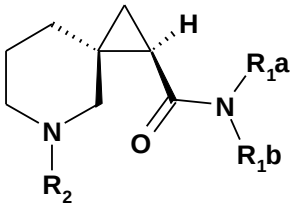
Beta-turn

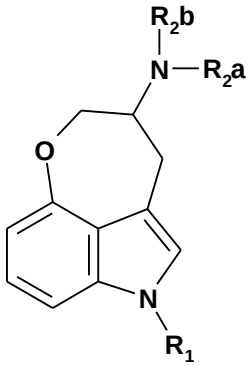


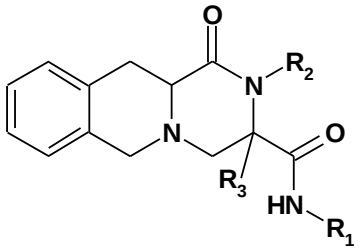
Gamma-turn

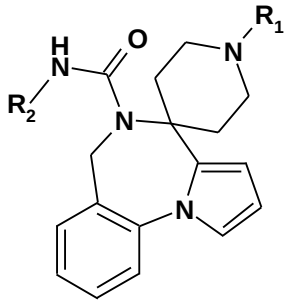
~ 350 new scaffolds proposed; Library contains 30K compounds

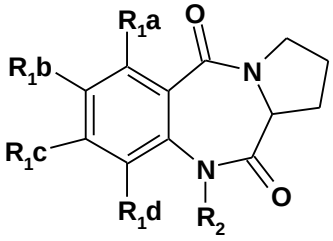
Examples of Scaffold (gamma-, beta-turns, dipeptide mimetics)

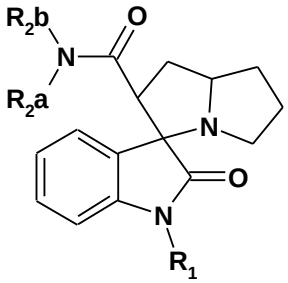


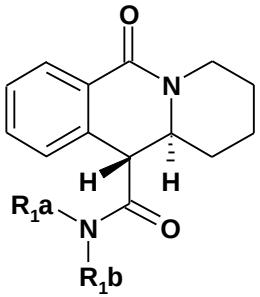


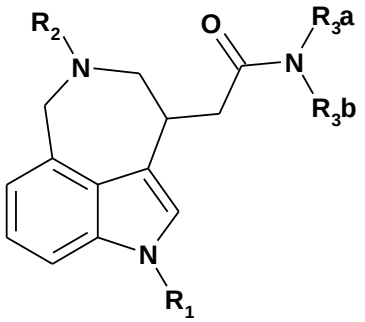


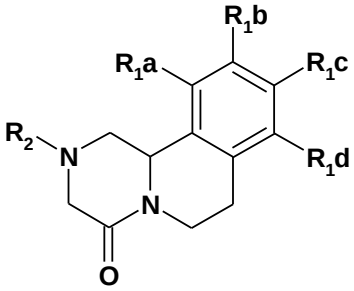


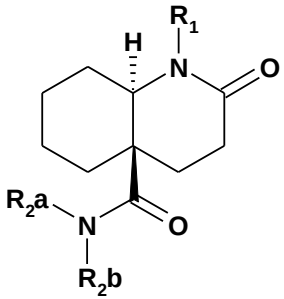


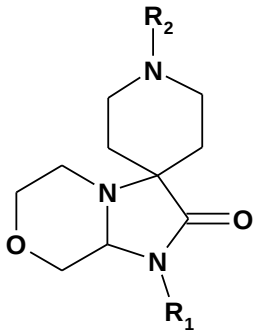


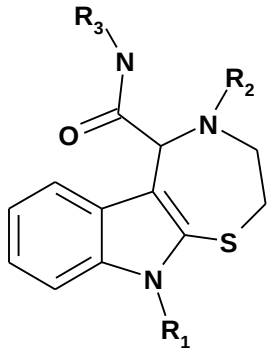








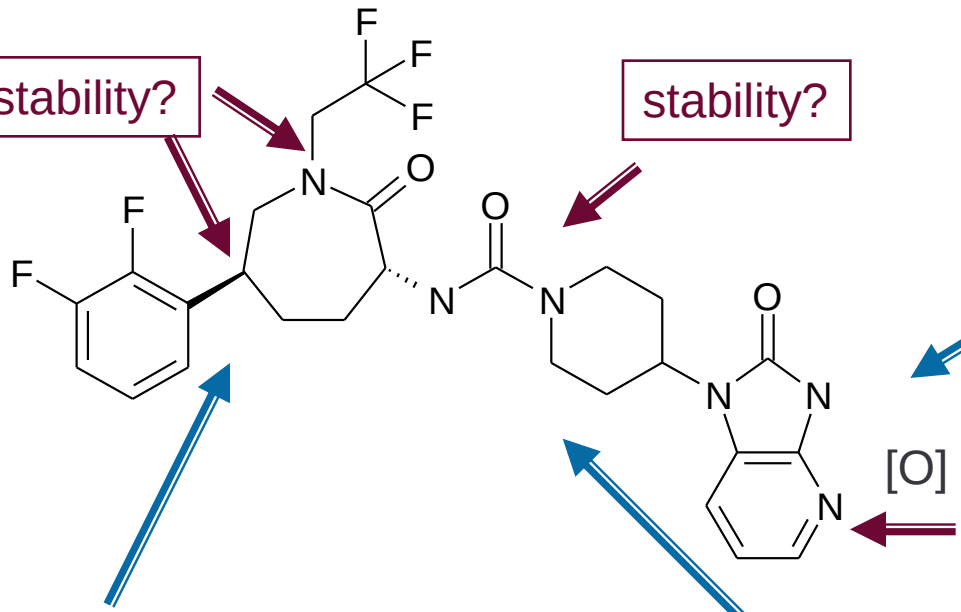




CGRP Antagonist

ChemDiv Proposal

Morphing of Telcagepant Structure



Variation of aza-heterocycle;
Bioisosteric replacement;
Variation of basisity, lipophilicity, solubility, number of HB-acceptors

Metabolically unstable nitrogen!
N-Oxide is the main metabolite

Variation of core heterocycle;
Variation of size and flexibility of heterocycle;
Variation of Aryl substituents;
Variation of N-substituent;
Are several fluorines needed?

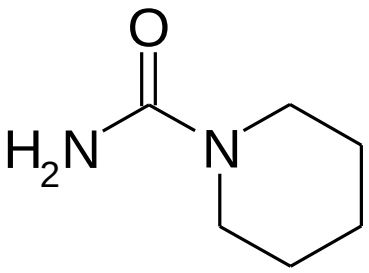
Variation of “linker”; urea bioisosters;
Variation of flexibility, lipophilicity, number of HB-acceptors and HB-donors

Telcagepant (Merck & Co.)
phase III – discontinued

The main point is the susceptibility of Telcagepant to oxidative metabolism, which is believed to be involved in hepatic toxicity. Bioorg Med Chem Lett 2009; 19 (22): 636

Set of compounds with Recognition Elements

Fragments of CGRP Antagonists
Inspiration for scaffold design



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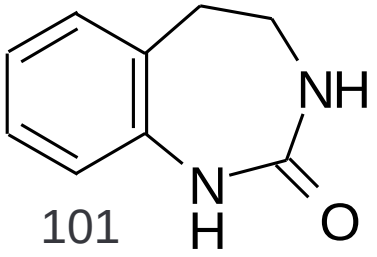

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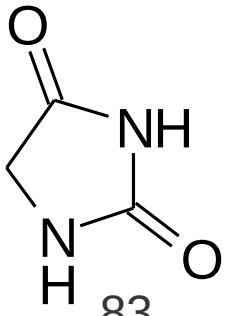

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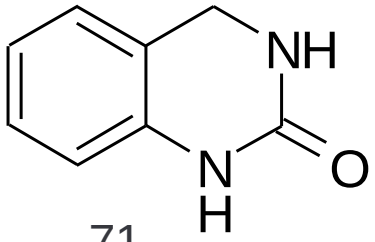

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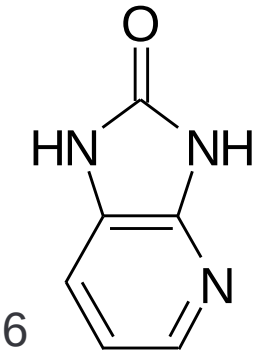

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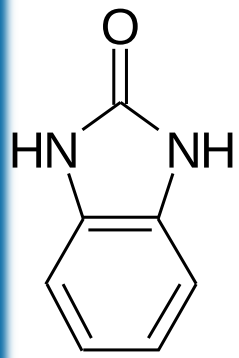

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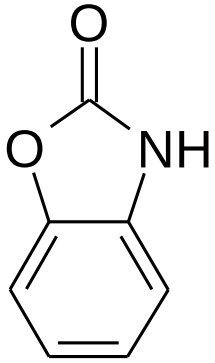

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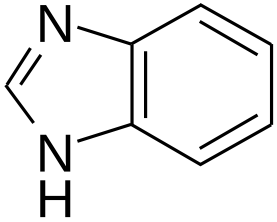

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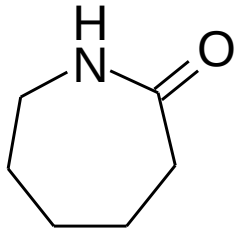

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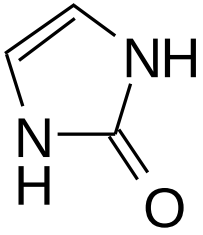

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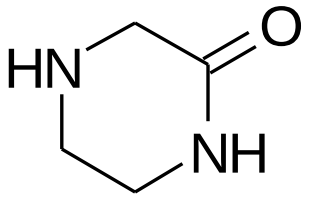

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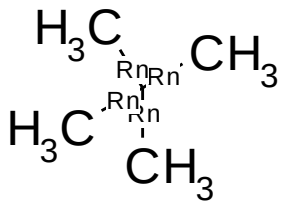
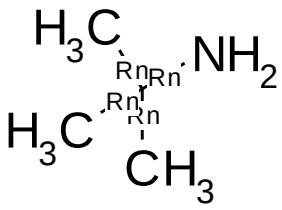
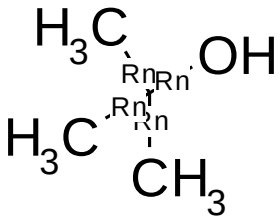


Spiro 103



Spiro 99



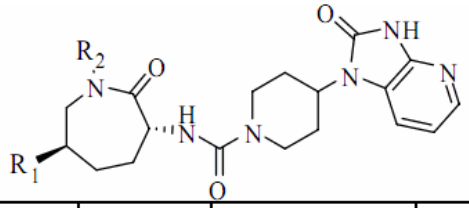
Spiro 18

Fluorine:
F – 151
2F – 138
3F – 107
4F – 19
6F - 2

The most privileged assembling sub-structures
(results of analysis of 510 antagonists)

Inspiration for substitution design

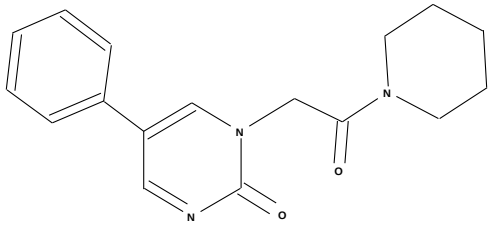
Potency and bioavailability for caprolactam CGRP receptor antagonists



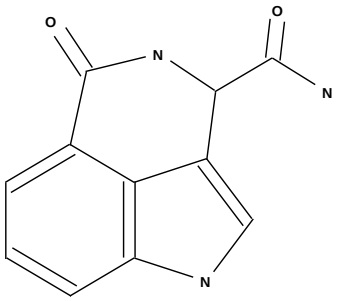
Compd	R_1	R_2	*Ki* (nM)	cAMP IC_{50} (nM)	cAMP +50% serum IC_{50} (nM)	Shift (fold)	Rat *F* (%)	Dog *F* (%)
6	Ph	H	83	520	700	1.3	NT	NT
7	2-F-Ph	H	22	65	120	1.8	NT	NT
8	3-F-Ph	H	51	220	250	1.1	NT	NT
9	2,3-diF-Ph	H	3.6	14	22	1.6	5	30
10	2,3-diF-Ph	2methoxyethyl	0.3	2	3	1.5	6	6
11	2,3-diF-Ph	2-hydroxyethyl	4.2	15	23	1.5	<1	NT
12	2,3-diF-Ph	cyclopropylmethyl	1.4	2	21	11	8	17
13	2,3-diF-Ph	methyl	2.7	8	22	2.8	12	60
14	2,3-diF-Ph	ethyl	2.4	6	30	5	30	61
15	2,3-diF-Ph	2-fluoroethyl	1.4	5	10	2	17	14
16	2,3-diF-Ph	2,2-difluoroethyl	0.9	5	15	3	25	11
17	2,3-diF-Ph	2,2,2,-trifluoroethyl	0.77	2.2	11	5	20	35

The American Chemical Society Prospective Conference Series “PK/PD for Medicinal Chemists” was held in Cambridge, MA on September 7-9, 2008. “CGRP Receptor Antagonists for the Treatment of Migraine” Ian M. Bell, Merck Research Laboratories, West Point, PA

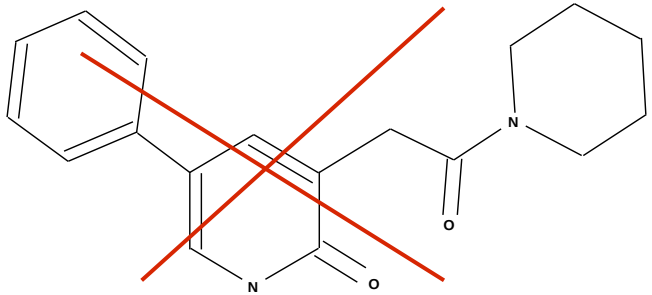
IP Assessment: SciFinder search



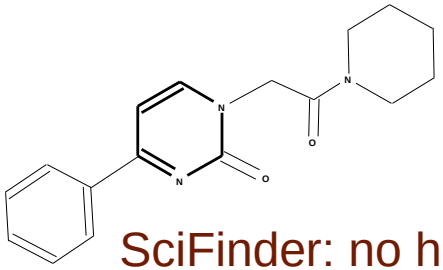
SciFinder: no hit found!



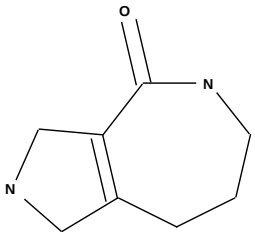
6 hits, not relative to CGRP



11 hits, all CGRP antagonists



SciFinder: no hit found!



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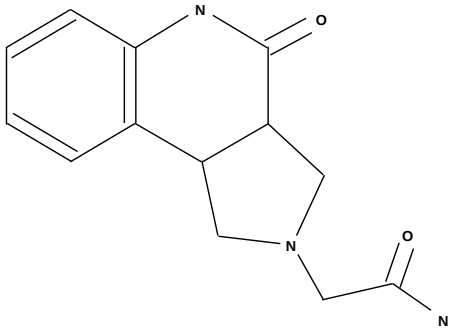
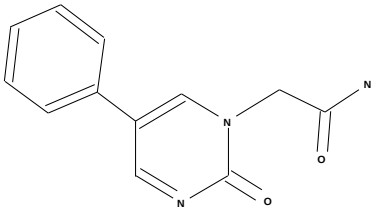
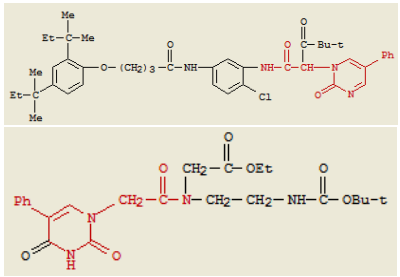
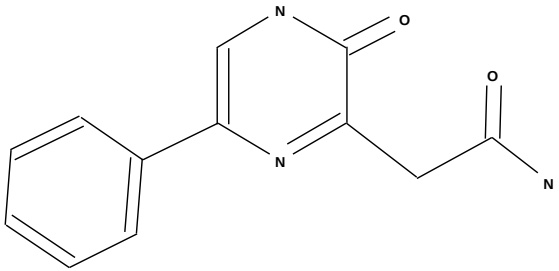


SciFinder: no hit found!!!



2 hits, not relative to CGRP





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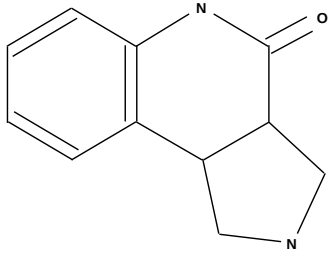
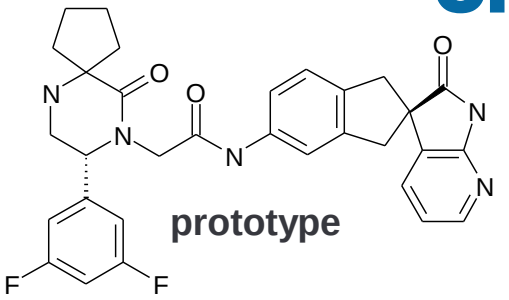
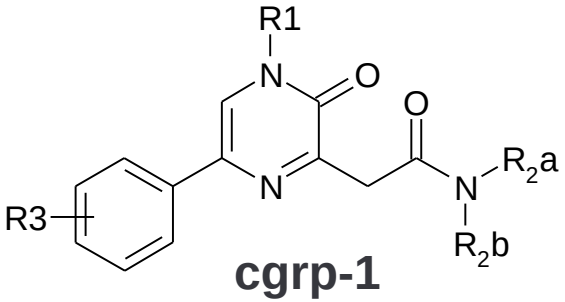


72 hits, not relative to CGRP

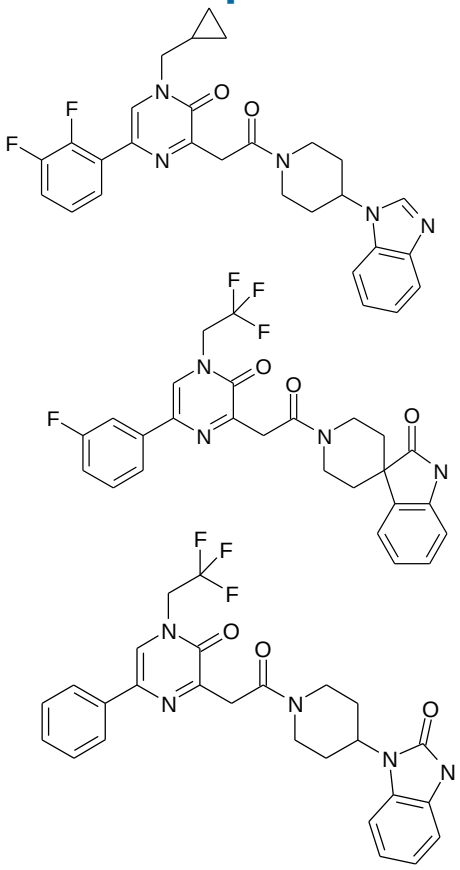
New Scaffold Design: cgrp-1 (example)
One from 10 series proposed

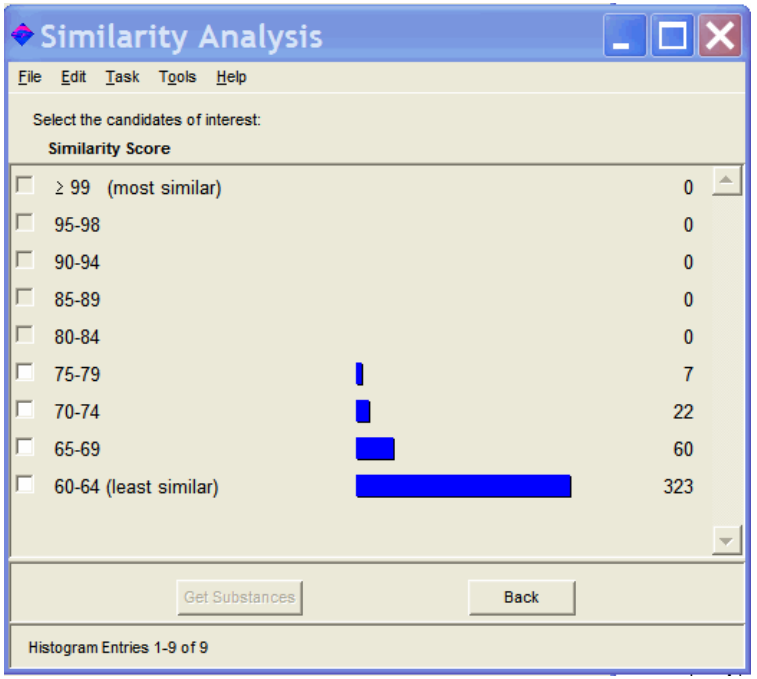




cgrp-1

Examples of compound:

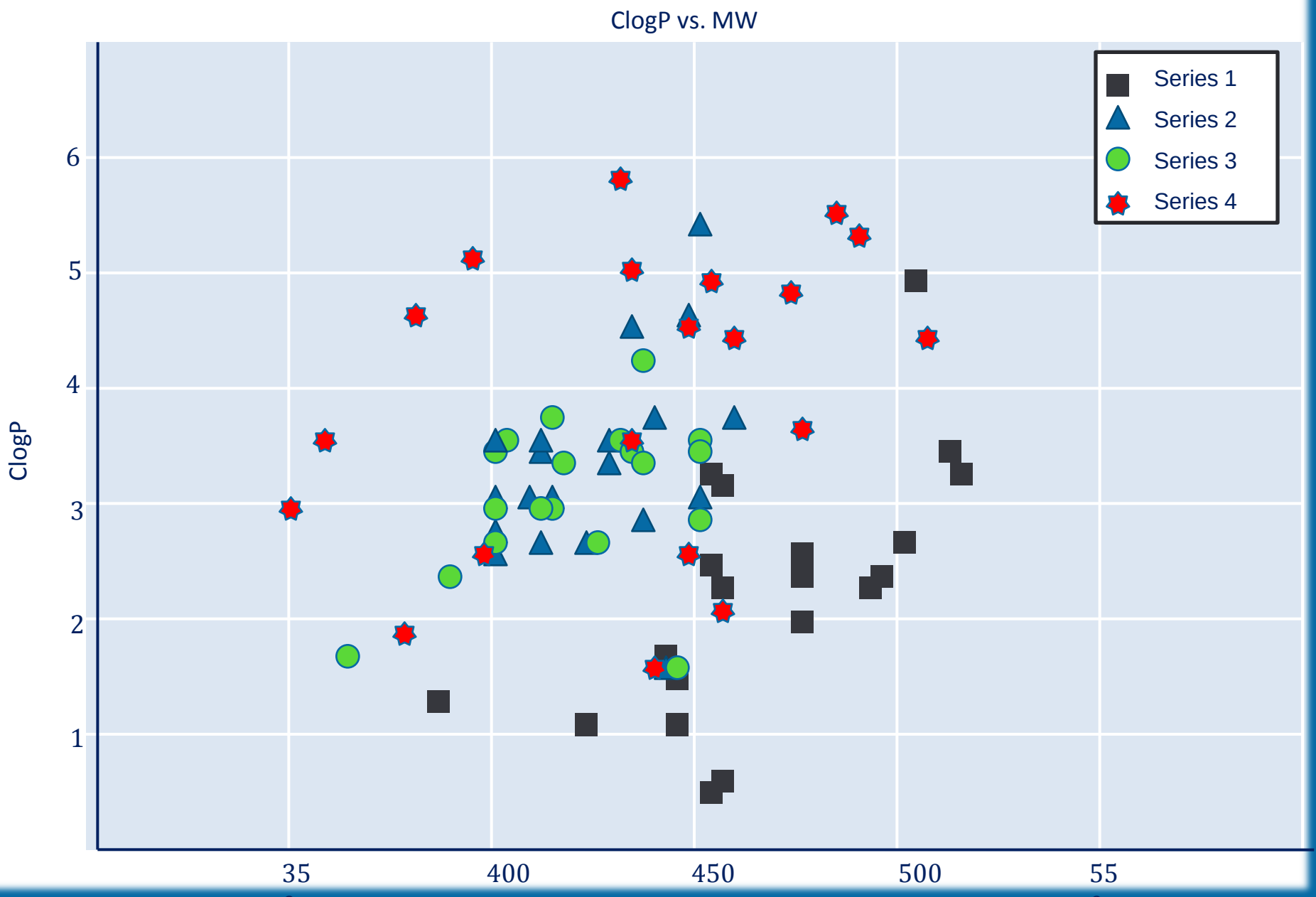




SciFinder Similarity Search
Summary for scaffold cgrp-1

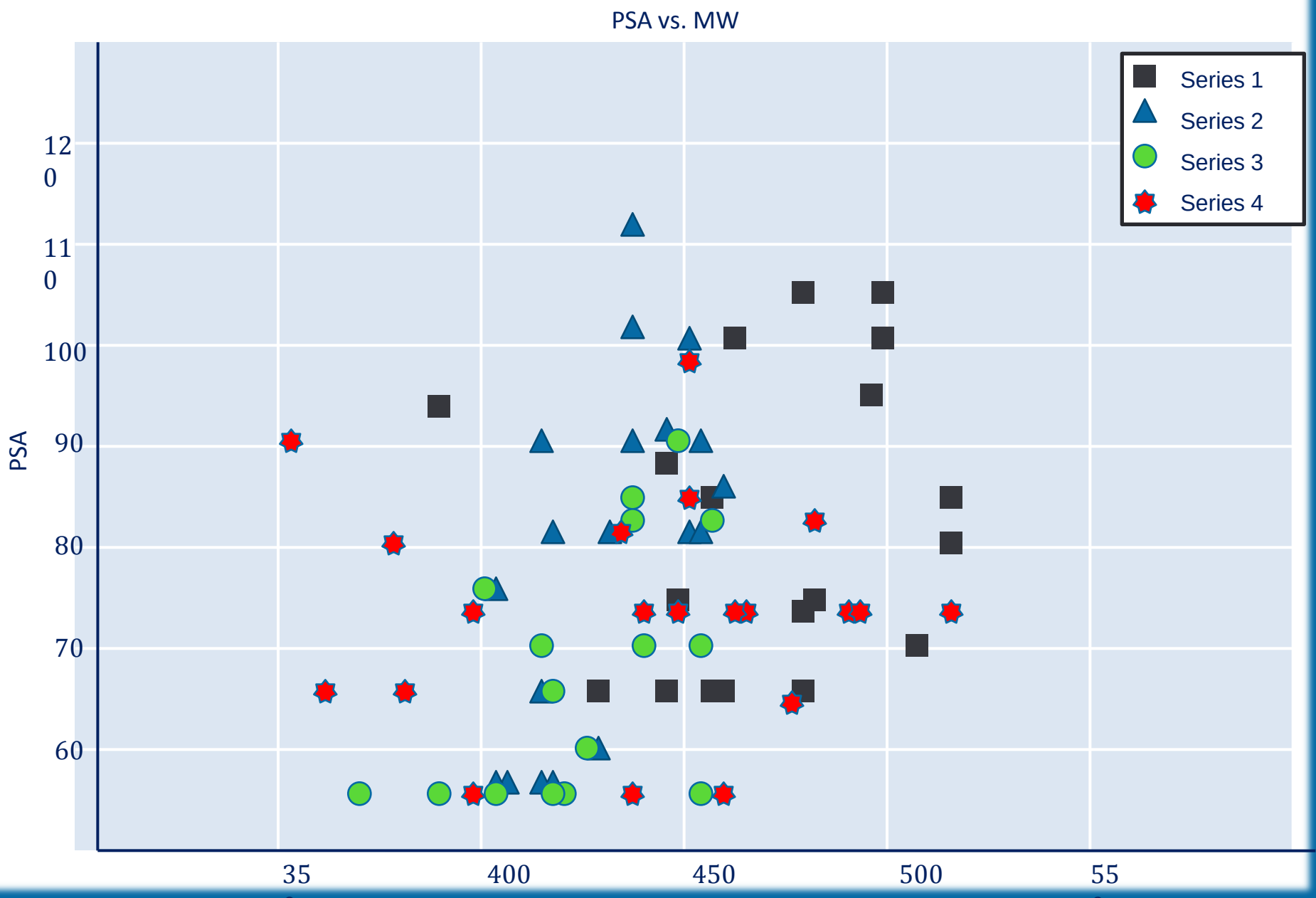
Property of Peptidomimetic Selected for Synthesis

ClogP vs MW



Property of Peptidomimetic Selected for Synthesis

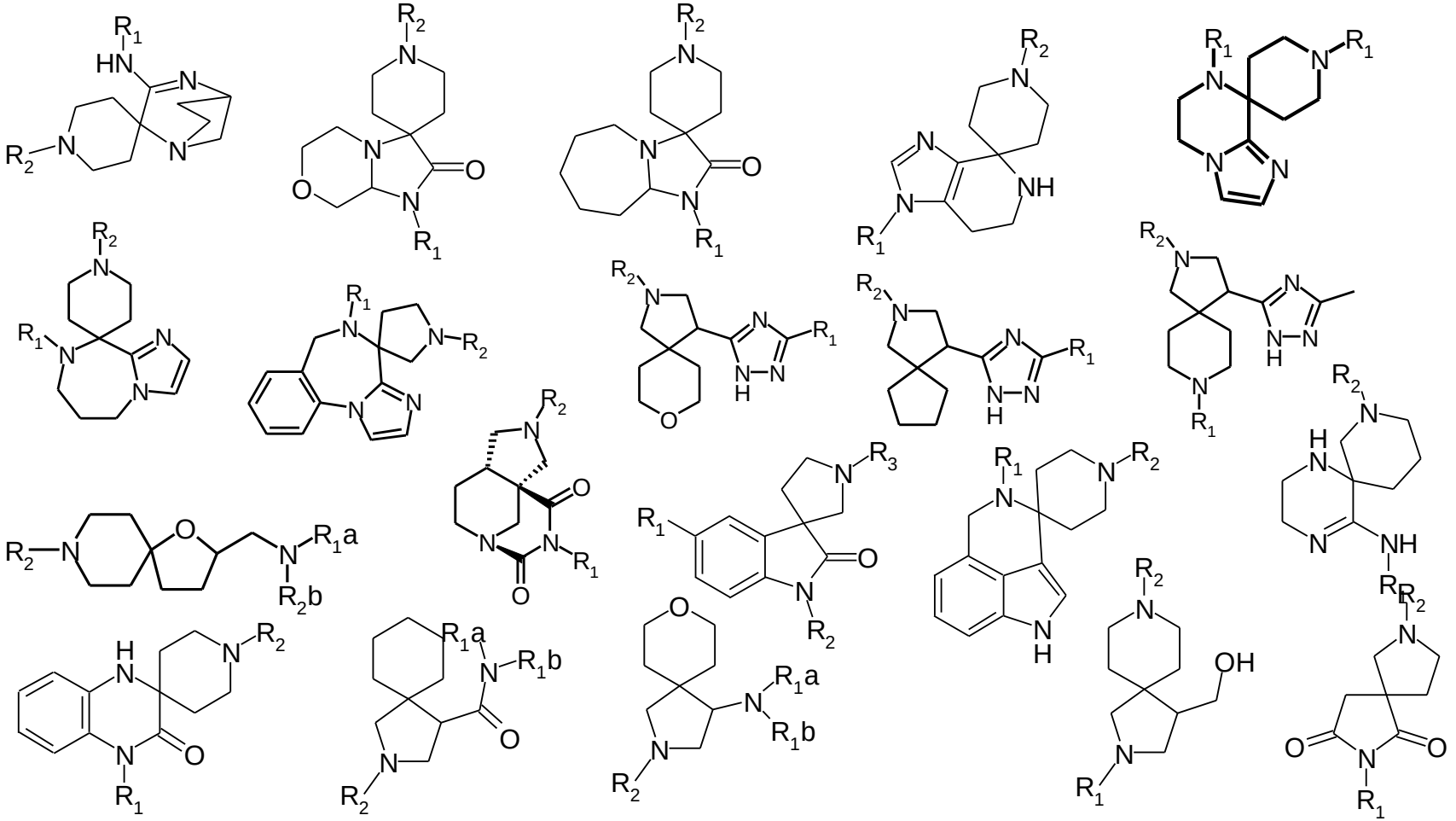
PSA vs MW



Spiro-Compounds Libraries for PPI Biased HTS

❖The goal of our work here is to provide a biologically relevant scaffold that allows for the incorporation of diversity elements that increase biological activity in targeted protein systems

❖We have developed new spiro-based scaffolds that has at least two diversity points that are spatially arranged by the spirocyclic nature of the scaffolding such that the diversity elements are precise



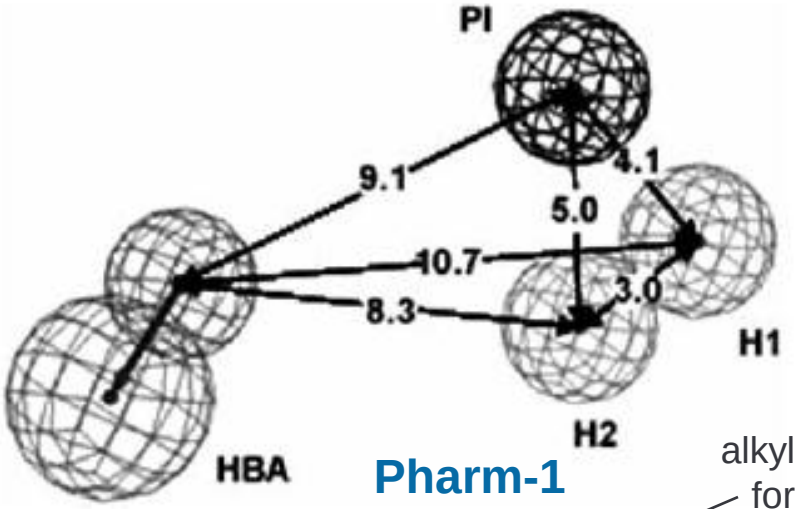
~ 350 new scaffolds proposed; Library contains 5.5K Spiro-compounds

Pharmacophore Model Generation for CCR1 antagonists

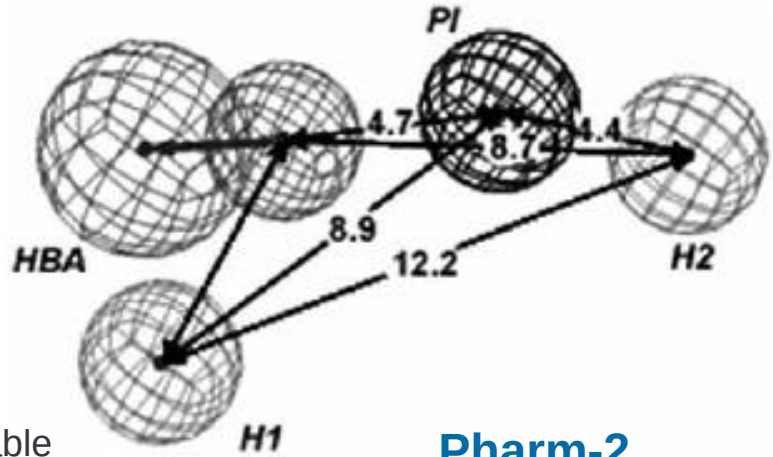
ChemDiv Proposal

Pharmacophore:

one hydrogen-bond acceptor, one positive ionizable and two hydrophobic groups



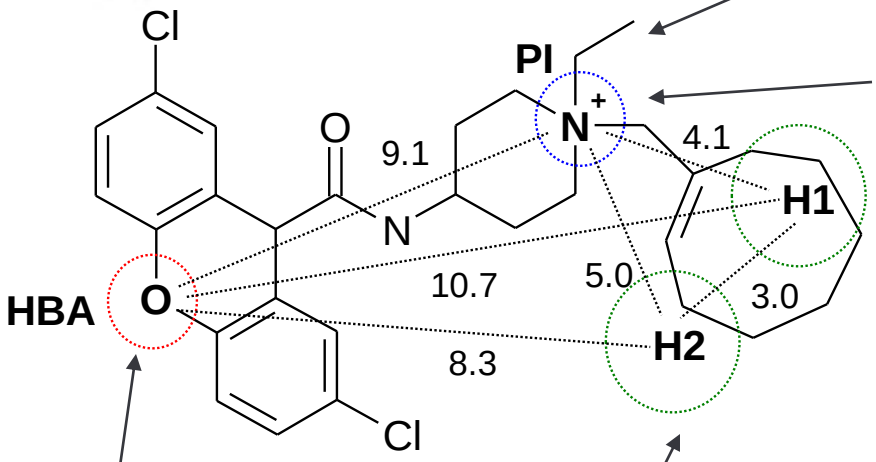
Pharm-1



Pharm-2

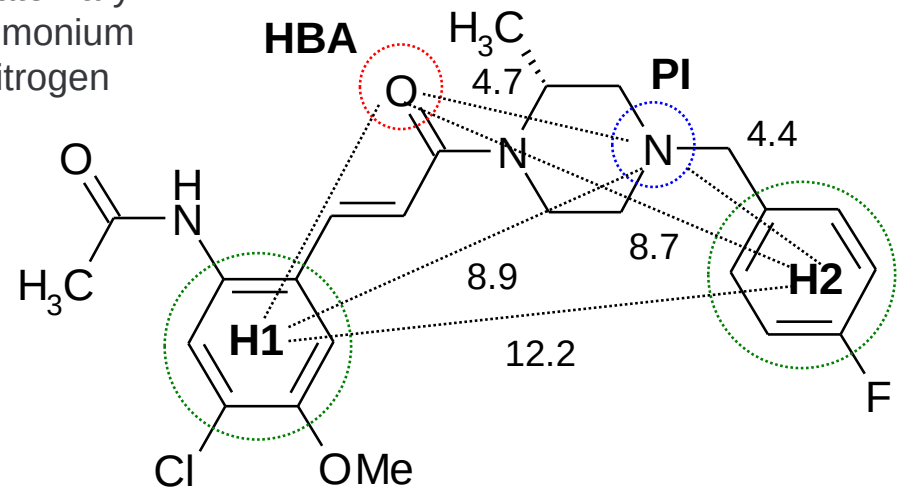
alkyl is preferable for the activity

quaternary ammonium nitrogen



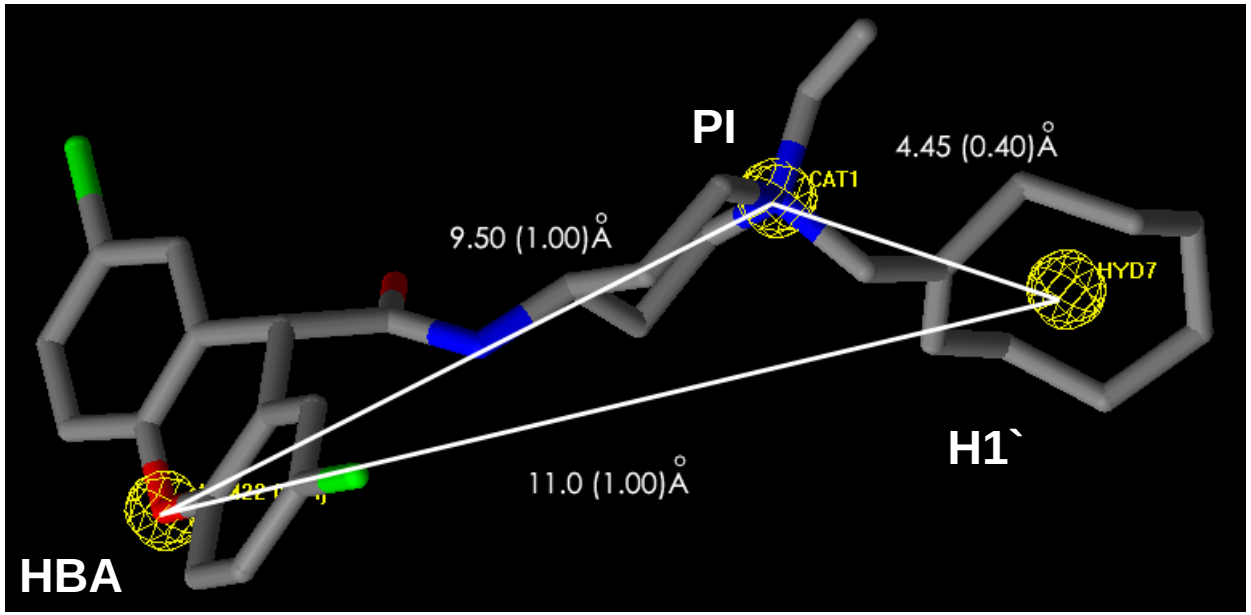
crucial for activity

cyclooctyl (or 1-cyclooctenyl) moiety mapped to the two hydrophobic features (H1 and H2), not Phe or Napht



3D-Pharmacophere Models for CC Chemokine Receptor 1 Antagonists. Medicinal Chemistry, 2009, 5, 318

ChemDiv Pharmacophore Models



three-centered pharmacophore:

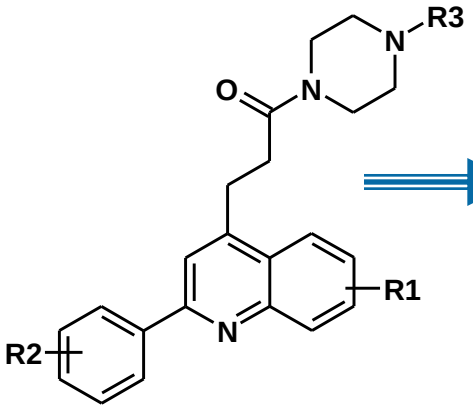
distances between HBA and PI as well as HBA and H1 are the same as for Pharm-1;

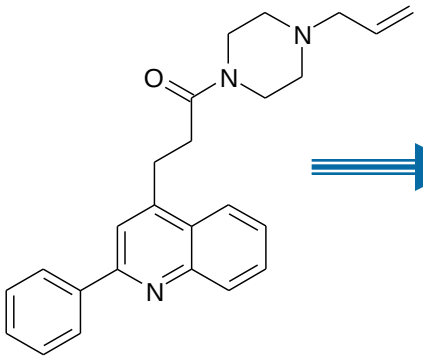
► the distance between PI and H1` is slightly longer than for Pharm-1, therefore H1` is positioned right between H1 and H2 covering the both hydrophobic areas;

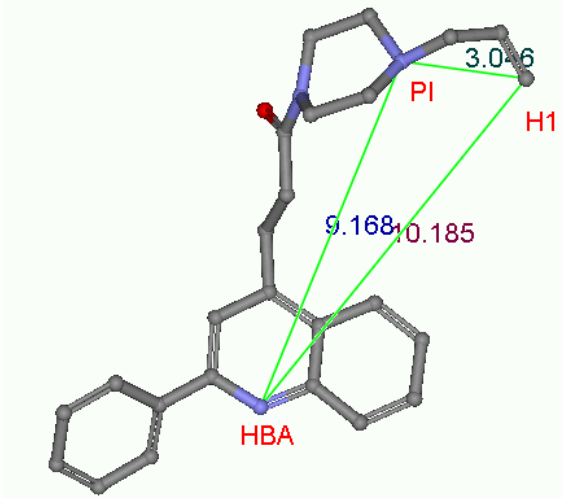
► prediction power is quite comparable with Pharm-1; this Pharmacophore is currently under evaluation and optimization;

► ChemDiv Pharmacophore is similar to Pharm-2

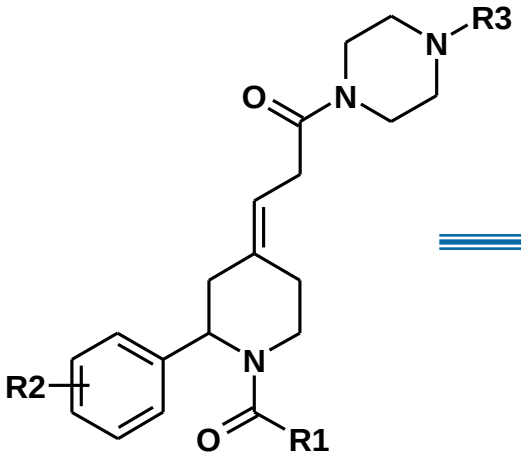
Scaffold Design According to Pharmacophore -1

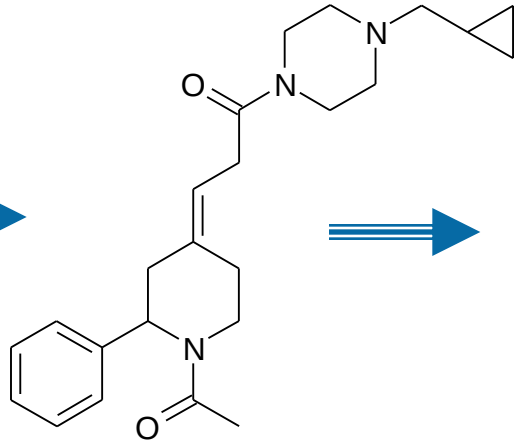


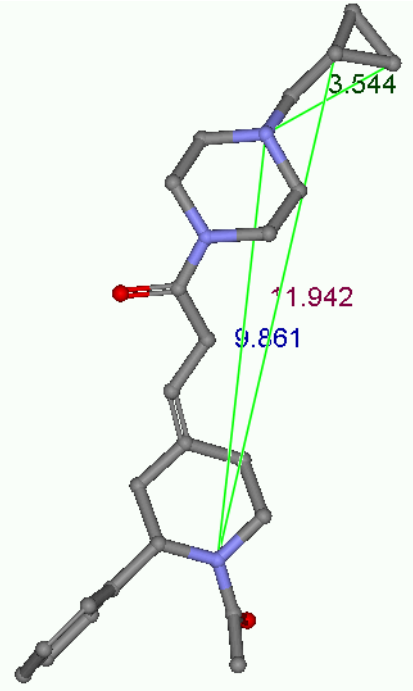




ccr1-1



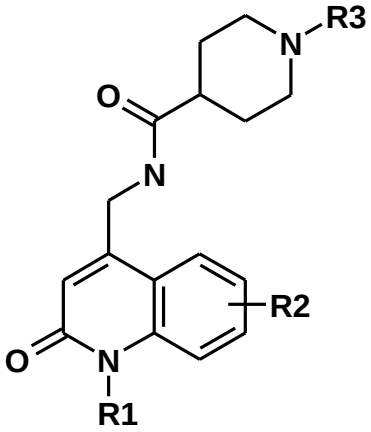




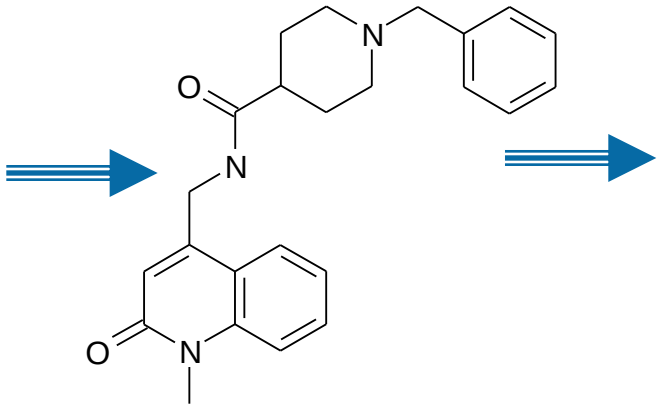
ccr1-2

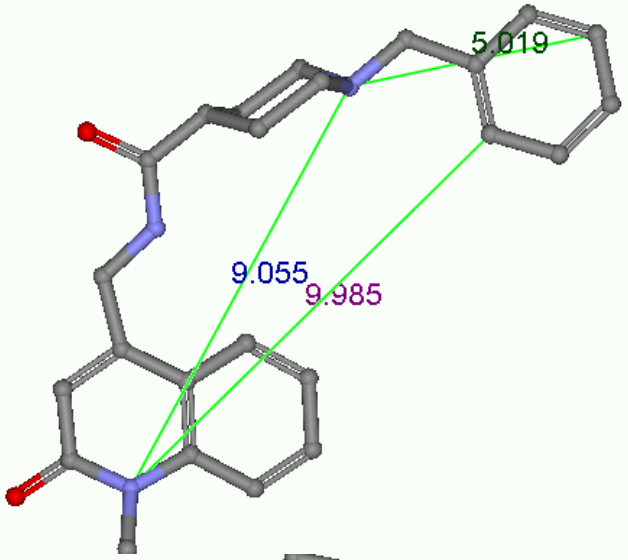
ChemDiv Proposal

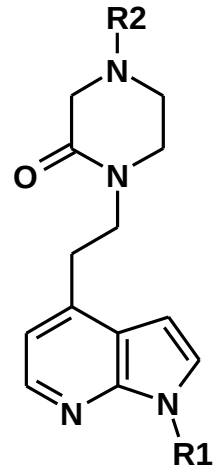
Scaffold Design According to Pharmacophore -2



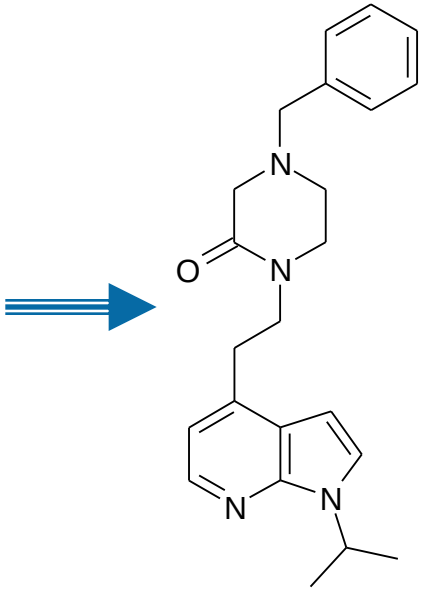
ccr1-3



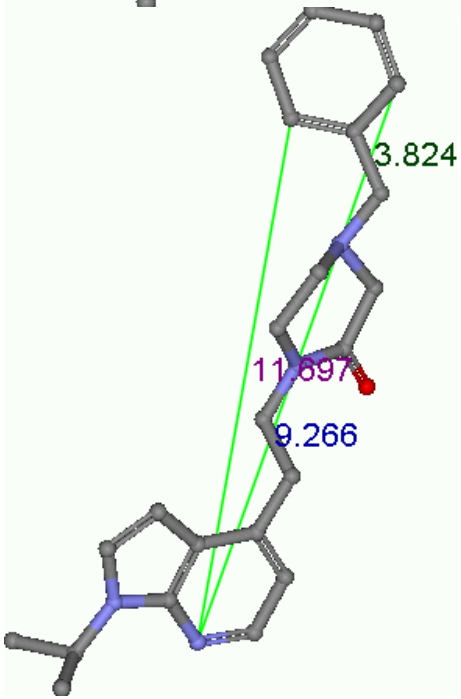




ccr1-4



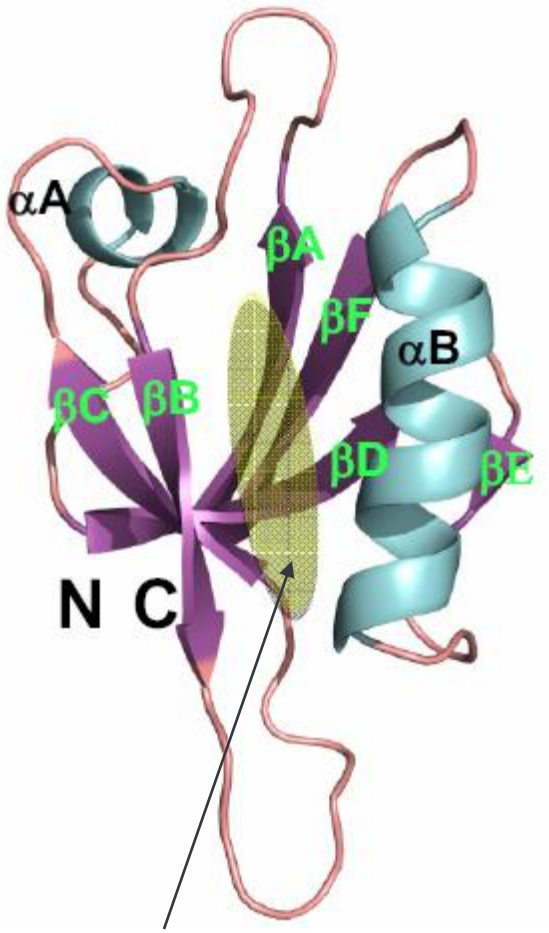
ChemDiv Proposal



Inhibitors of PDZ-domain mediated PPI

PDZ domain-containing proteins

more than **200** structures of PDZ domains (~80-100 AA) - either the PDZ domains alone, their complexes with binding partners, or PDZ-PDZ dimers - have been determined by NMR and X-ray crystallography



Binding site is in the groove between the β1 strand and the α3 helix structures

CANONICAL PDZ DOMAINS

PDZ domains are usually composed of 5 or 6 β-strands (βA ~ βF), a short α-helix (αA) and a long α-helix (αB);

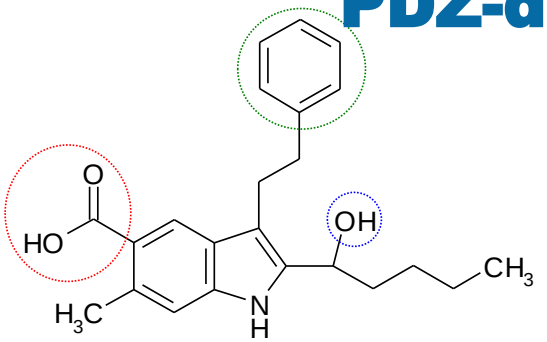
► the ***N***- and ***C***-termini of canonical PDZ domains are in proximity to each other on the opposite side from the peptide-binding site in a *groove* between the αB-helix and βB-strand structures

► the binding site in the *groove* shares a highly conserved carboxylate-binding loop (**R/K-XXX-G-Φ-G-Φ** motif, where **X** is any amino acid residue and **Φ** is hydrophobic residues located before the βB strand). **This loop region of PDZ domain plays a key role in ligand binding**

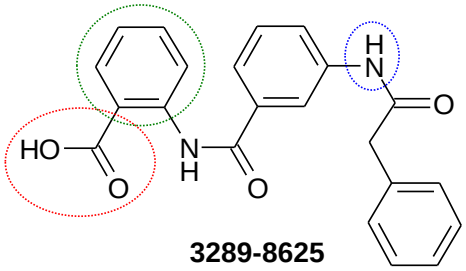
► a highly conserved positively charged residue (*e.g. Arg318* of PDZ) and the main chain amides of the **–GΦGΦ–** motif form hydrogen bonds with the terminal carboxylate group of C-terminal ligand side

Lee and Zheng Cell Communication and Signaling 2010, 8:8

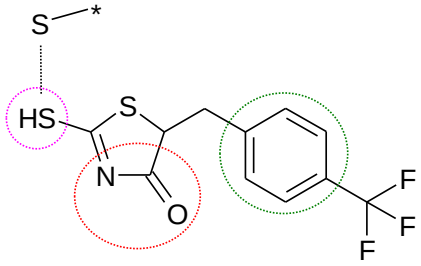
Examples of small-molecule inhibitors of PDZ-domain mediated PPI



FJ-9
Preclinical
University of California

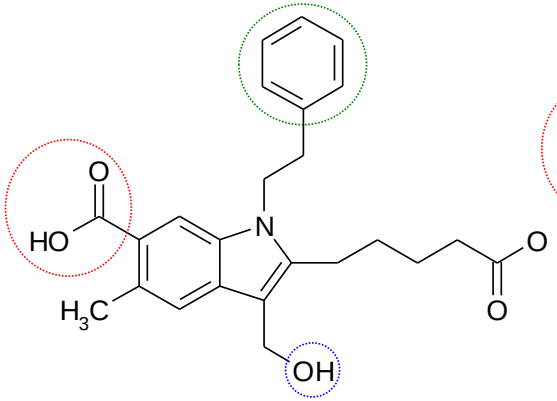


3289-8625
Compond from
ChemDiv stock

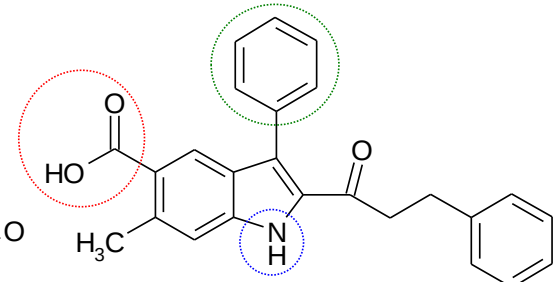


439013
Biological Testing
Combinature Biopharm

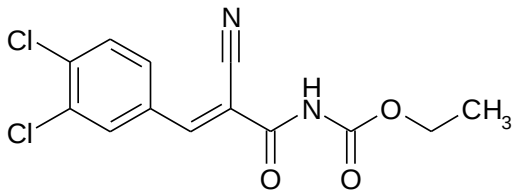
2EXG



632545
Biological Testing
St Jude Children's Research Hospital



635302
Preclinical
University of California

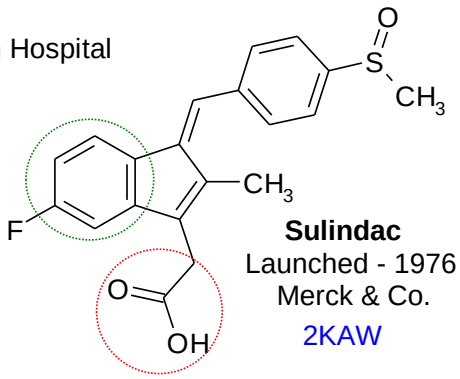


645205
Biological Testing
NeuroSearch

H-bond acceptors

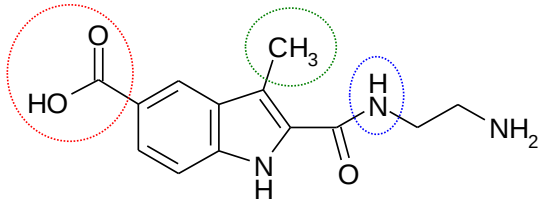
H-bond donors

hydrophobic moiety



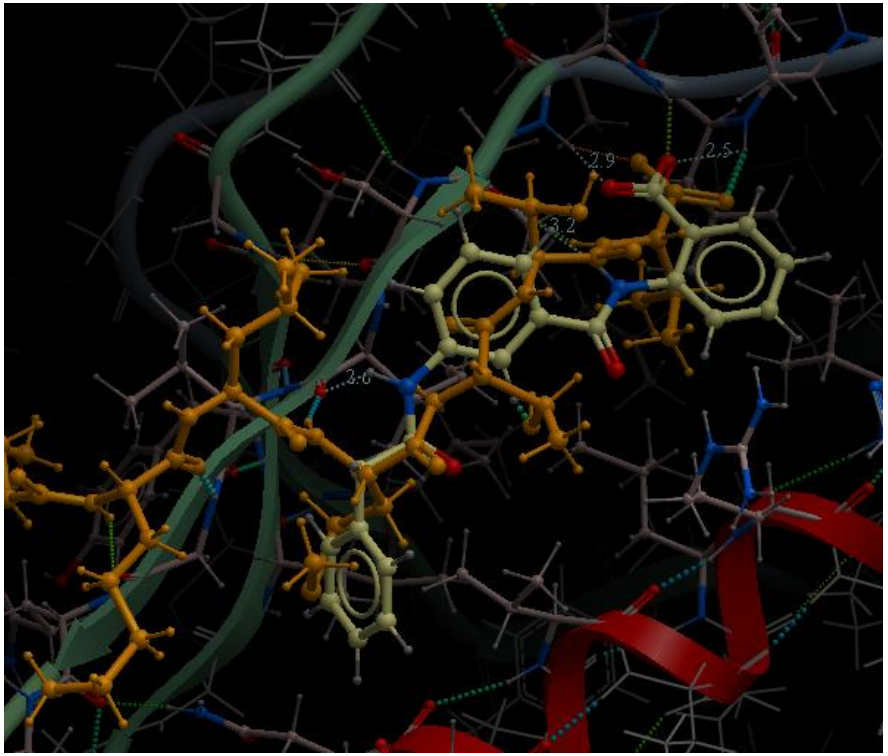
Sulindac
Launched - 1976
Merk & Co.

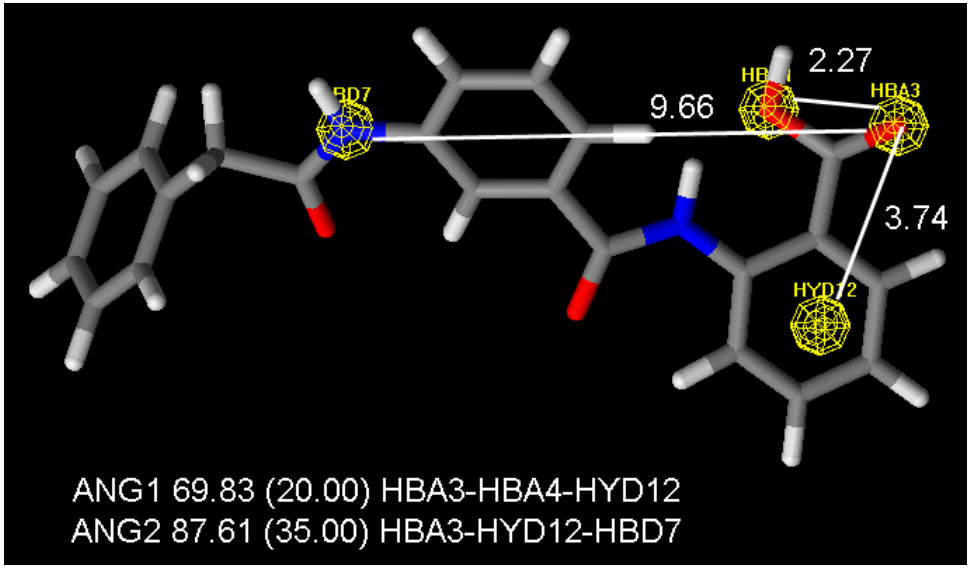
2KAW



748394
Biological Testing

ChemDiv PDZ Pharmacophore Models

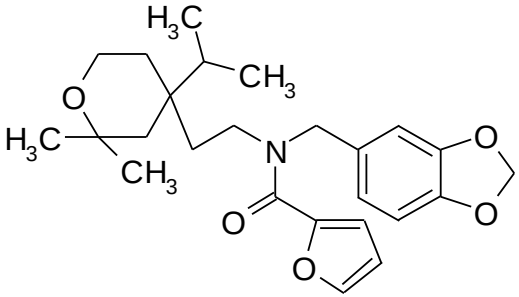


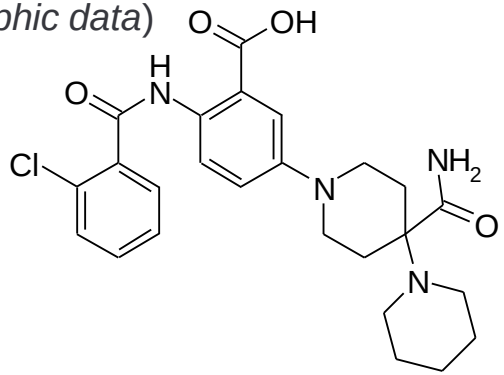


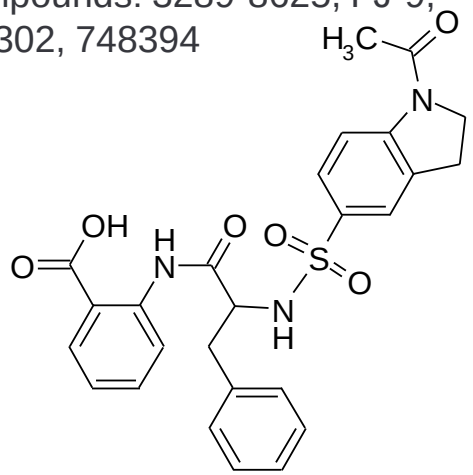
1st three-centered pharmacophore model mapped from **3289-8625**

matched compounds: 3289-8625, FJ-9, 632545, 635302, 748394

orange - Dapper peptide (*crystallographic data*)
yellow - 3289-8625 (*docking study*)





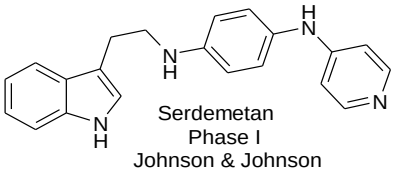


Compounds with high score

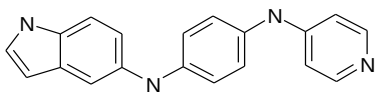
~ 250 new scaffolds proposed; Library contains 5.2K compounds

Inhibitors of MDM2/P53 interaction

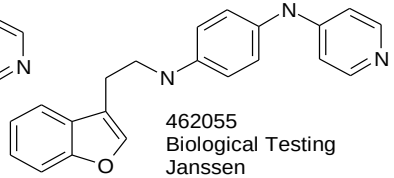
Representative examples of MDM2 small molecule inhibitors



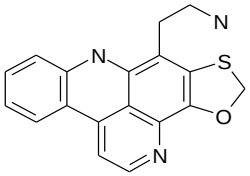
Serdemetan
Phase I
Johnson & Johnson



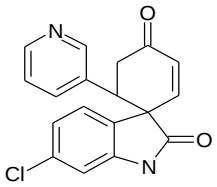
462056
Biological Testing
Janssen



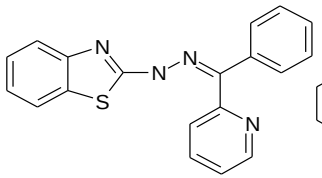
462055
Biological Testing
Janssen



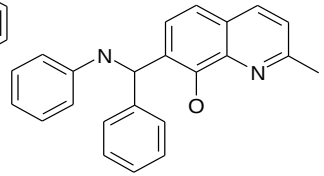
Lissoclindine B
Biological Testing
National Institutes of Health



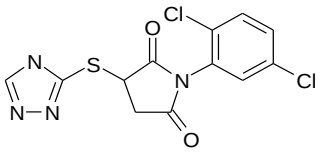
478102
Biological Testing
Roche



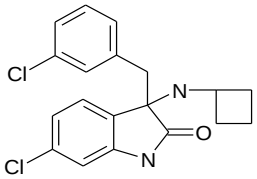
NSC-333003
Biological Testing
H. Lee Moffitt Center



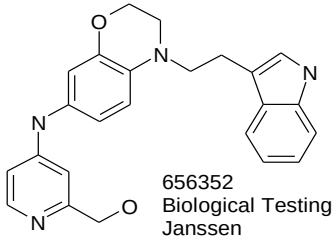
NSC-66811
Biological Testing
University of Michigan



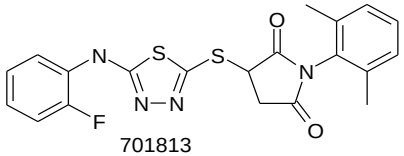
701815
Biological Testing
PharmaDesign



474774
Biological Testing
Roche



656352
Biological Testing
Janssen



701813
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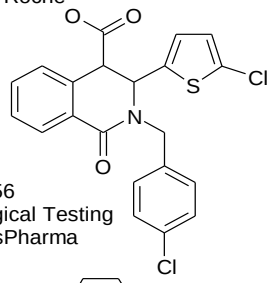
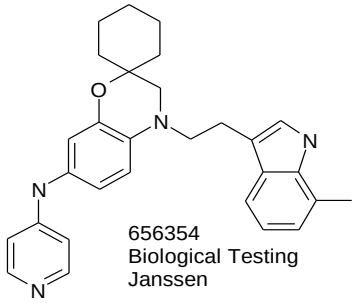
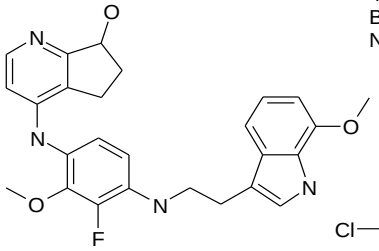


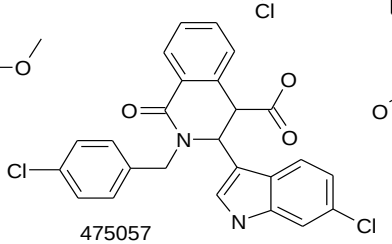
475056
Biological Testing
NexusPharma



656354
Biological Testing
Janssen



656344
Biological Testing
Janssen



475057
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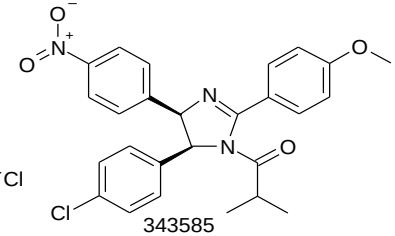
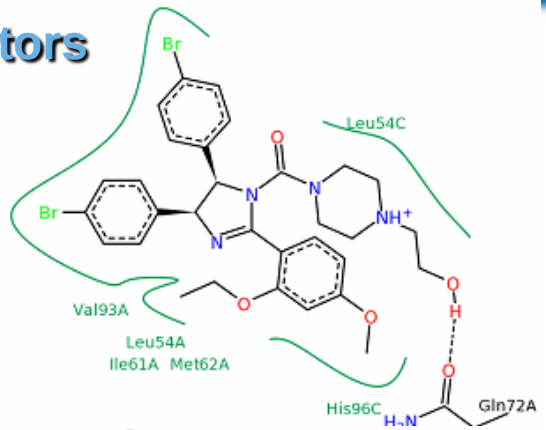
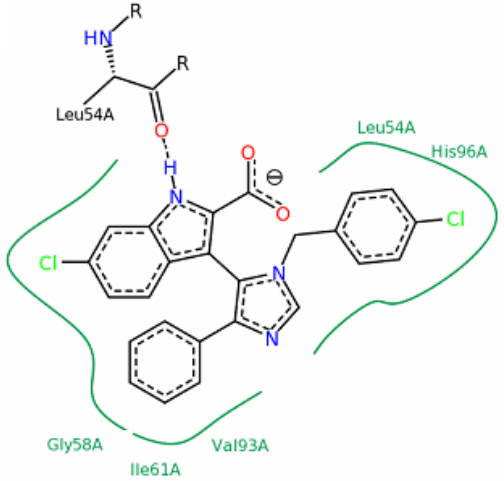
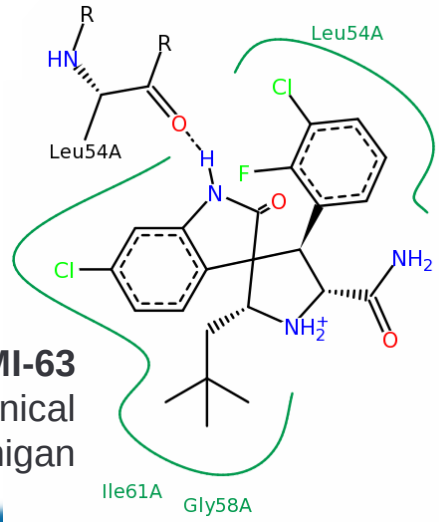


343585
Biological Testing
Roche



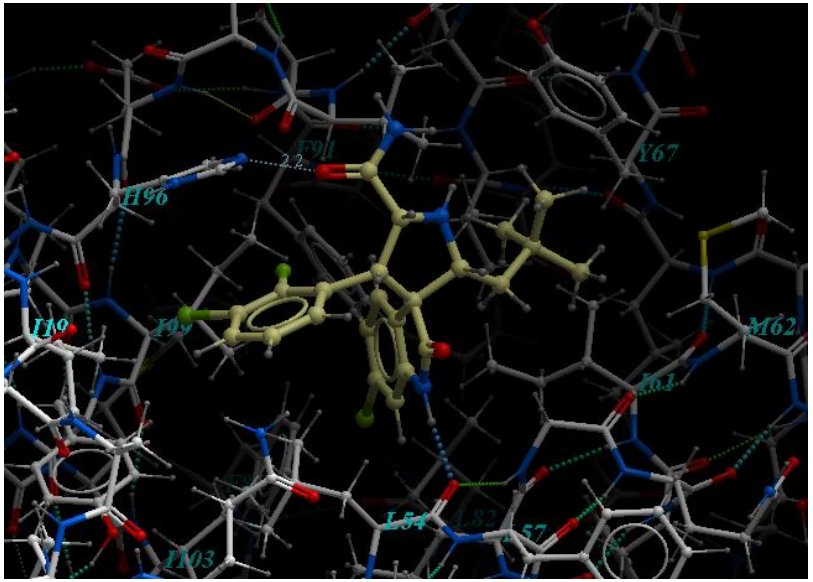


In active
MDM2/P53
binding site

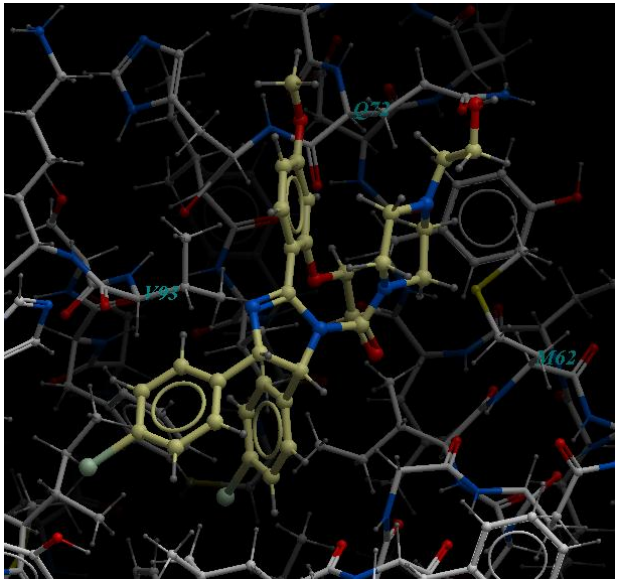


MI-63
Preclinical
University of Michigan

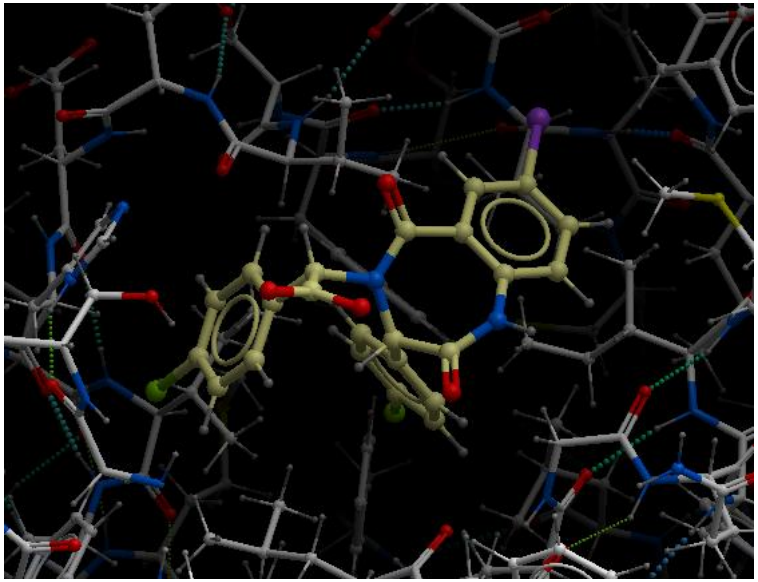
Examples of crystallographic data obtained for several MDM2 inhibitors



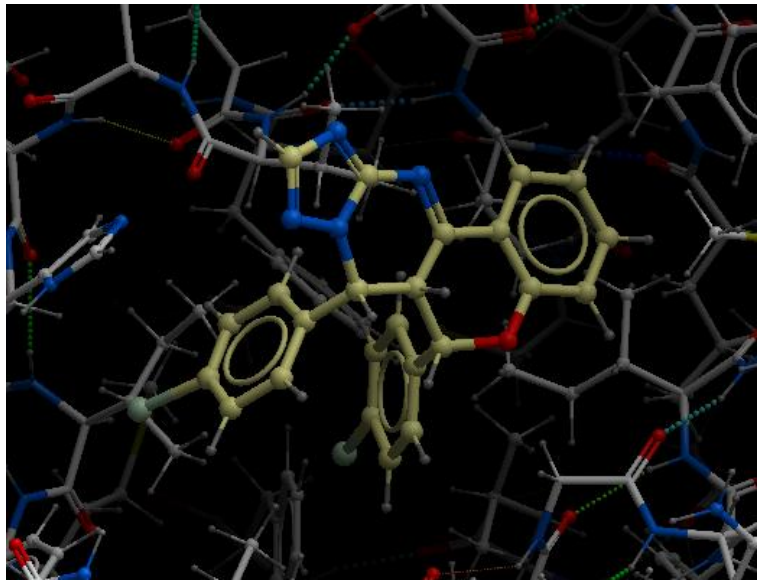
3LBL (MI-63)



1RV1

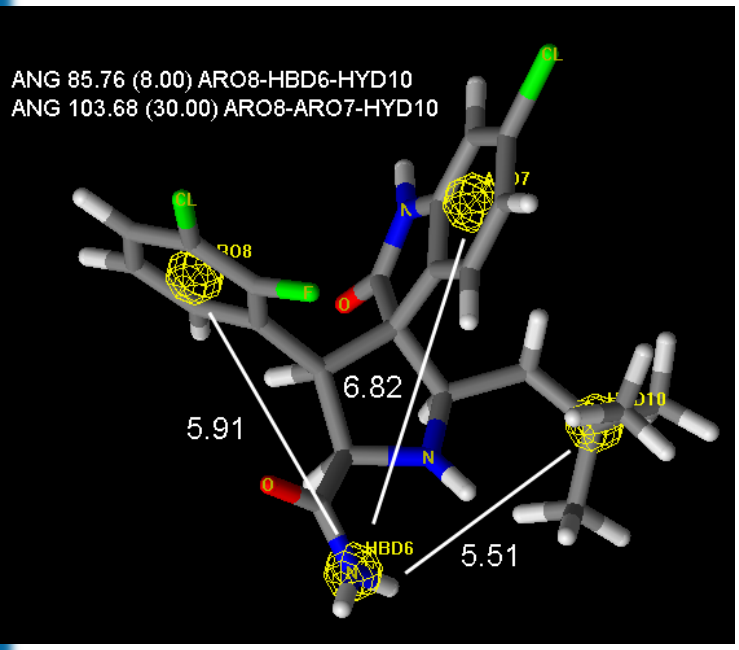


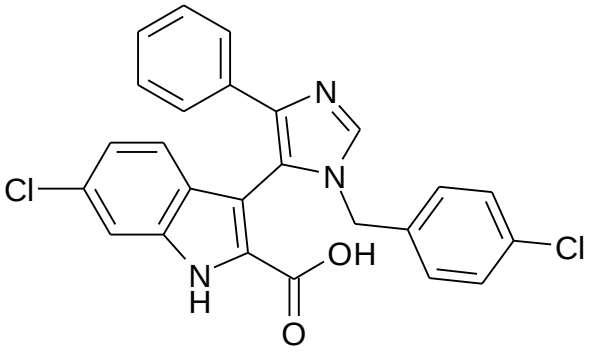
1T4E



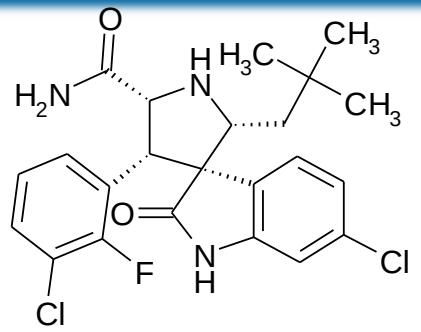
3JZK

1st four-centered MDM2 pharmacophore model mapped from **MI-63**



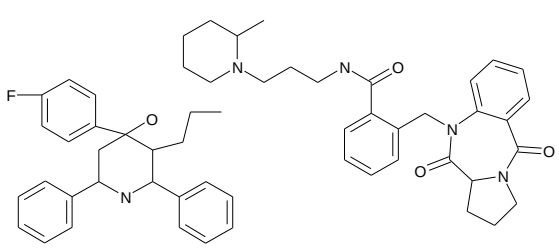


MI-63

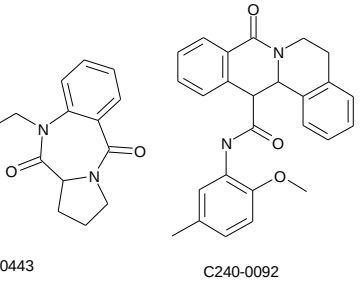


matched compound (example) – known MDM2 inhibitor

Representative examples of compounds successfully passed 1st MDM2 pharmacophore model

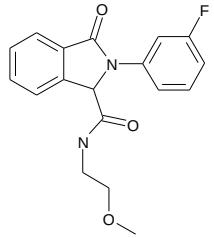


Y010-0045

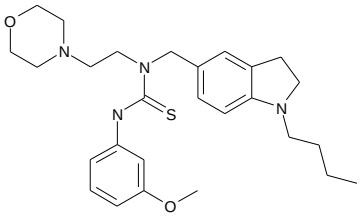


L610-0443

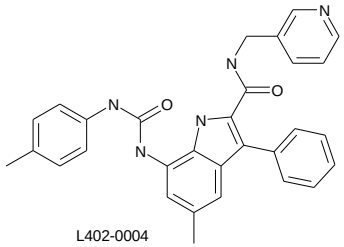
C240-0092



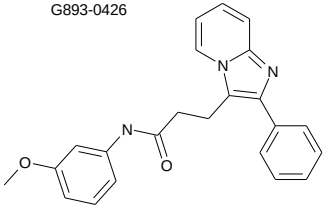
G893-0426



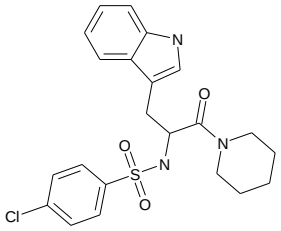
K788-5572



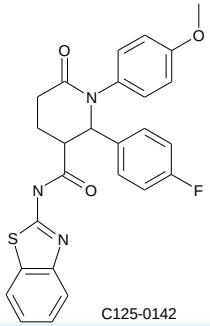
L402-0004



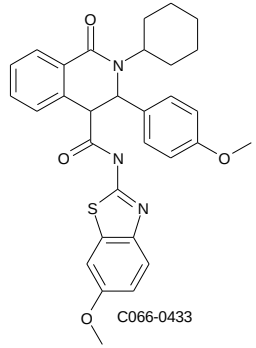
L609-2032



P772-0017

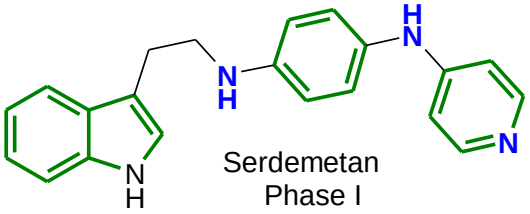


C125-0142

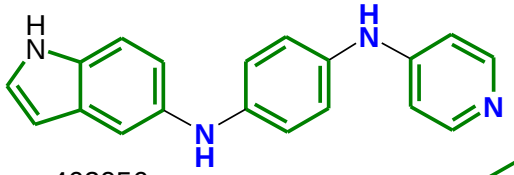


C066-0433

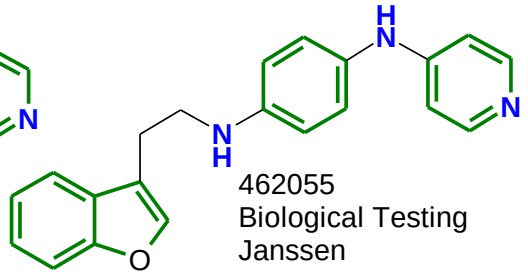
Topological pharmacophore for several MDM2 inhibitors



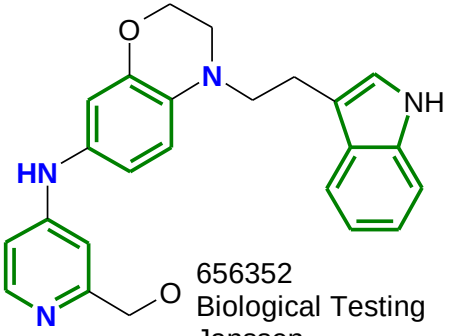
Serdemetan
Phase I
Johnson & Johnson



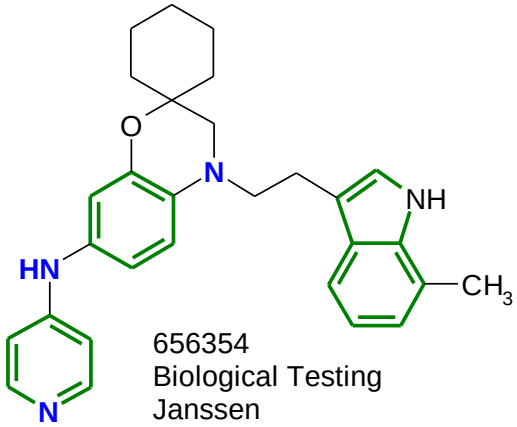
462056
Biological Testing
Janssen



462055
Biological Testing
Janssen



656352
Biological Testing
Janssen



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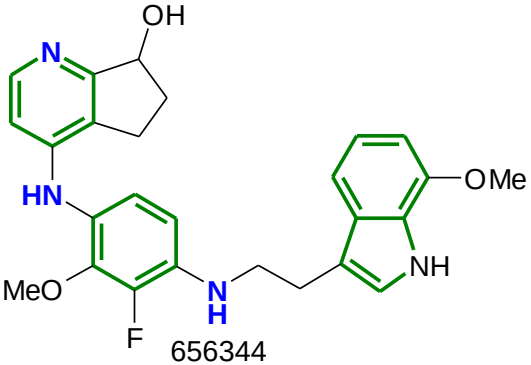
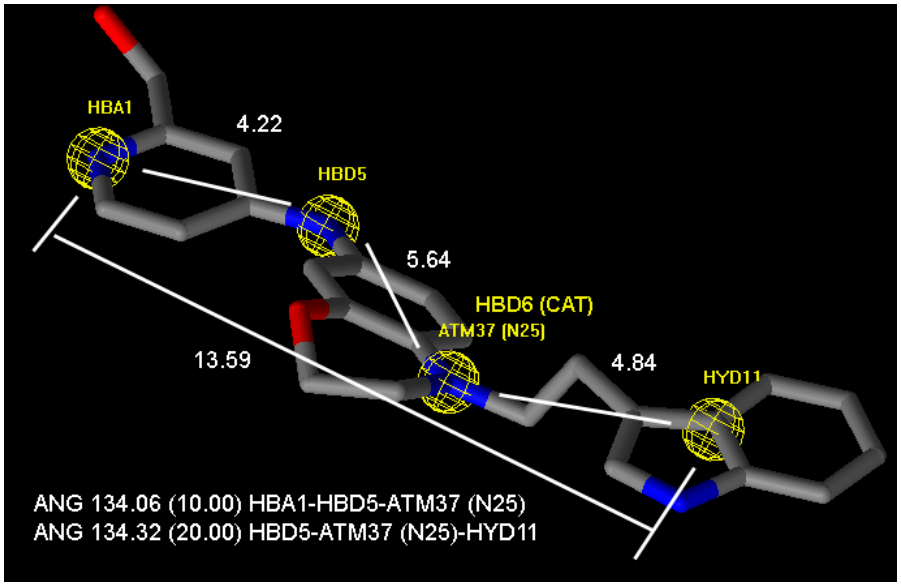


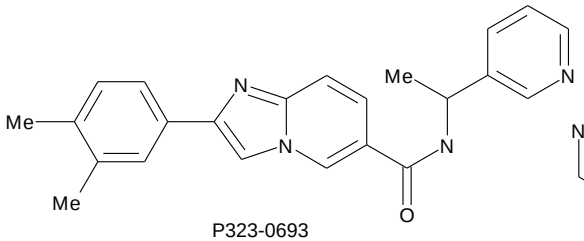
656344
Biological Testing
Janssen



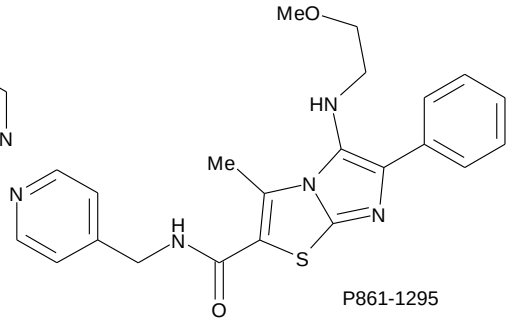
2nd four-centered MDM2 pharmacophore model mapped from 656352

all the presented compounds are mapped well

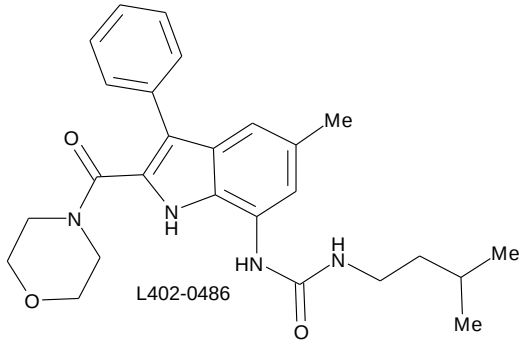
Representative examples of compounds passed 2nd MDM2 pharmacophore model



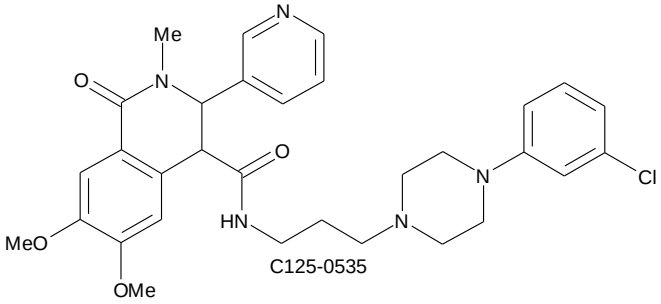
P323-0693



P861-1295



L402-0486



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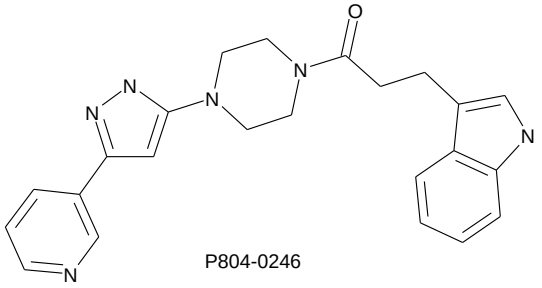

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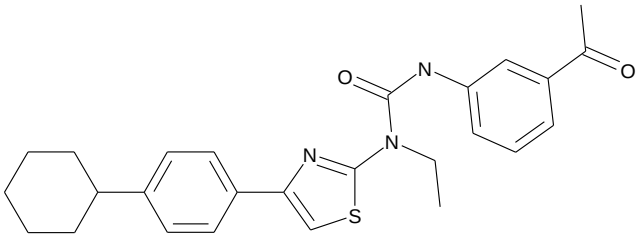

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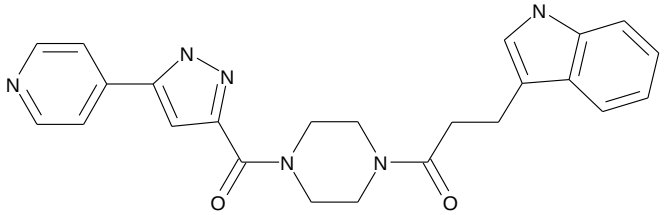
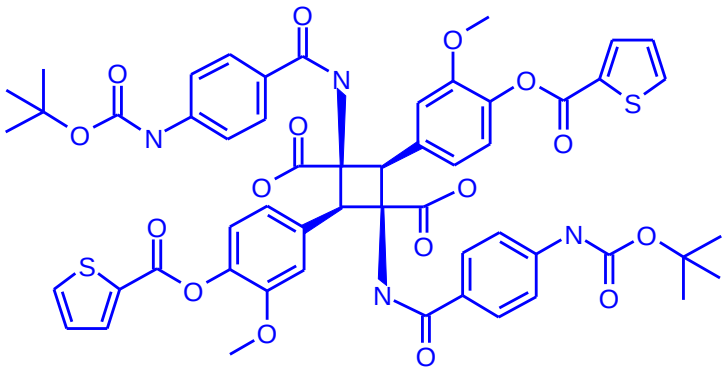


G639-3495

Other types of PPI Inhibitors

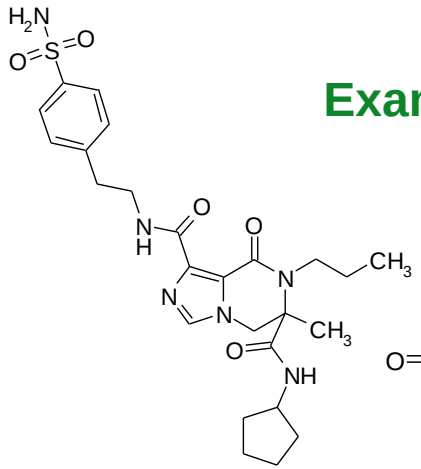
Set of Eccentric Compounds

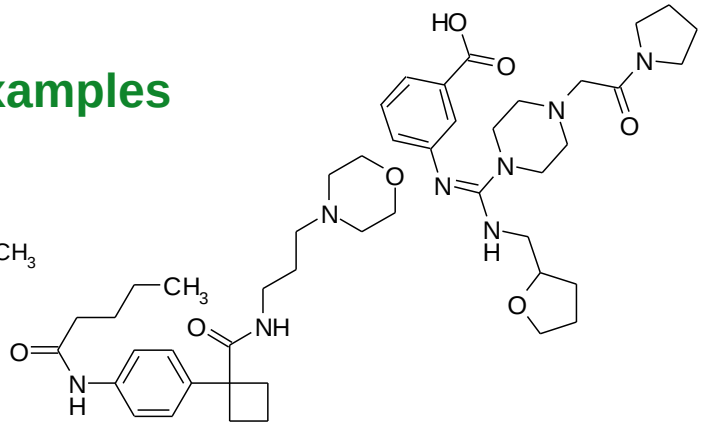
GLP-1 receptors represent the promising and the most poorly druggable PPI targets

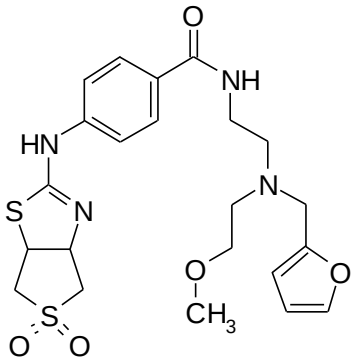


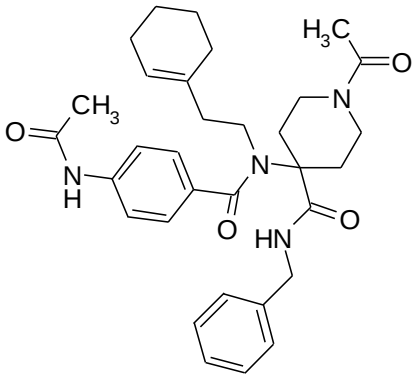
SH-7871 – peculiar GLP1 agonist

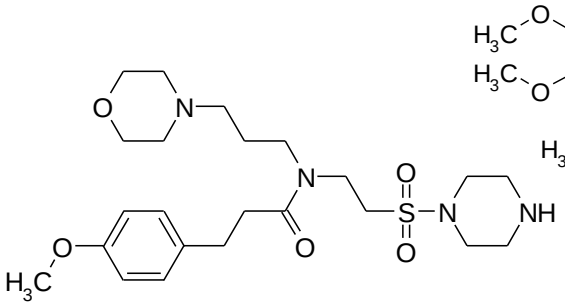
Examples

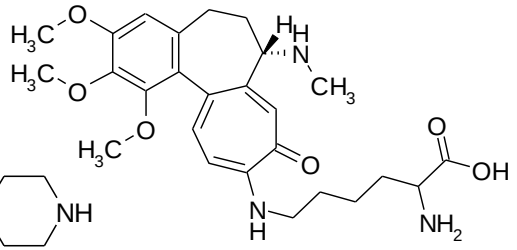












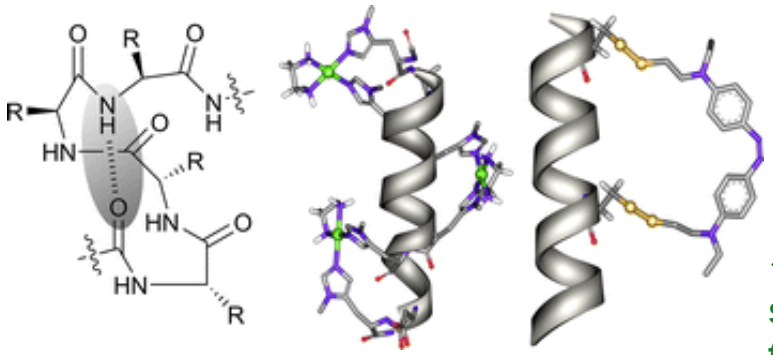
Sub-library contains 7.0K eccentric (nonreactive !) compounds

Contemporary medicinal chemistry faces diverse challenges from several directions, including the need for both potency and specificity of any therapeutic agent; the increasingly demanding requirements of low toxicity shown across all patients treated; and the need for novelty in intellectual property, given the extensive use of benzenoid and heteroaromatic ring systems in numerous patents. Increasingly, such challenges are being met by a shift to new and/or **unusual ring systems** (scaffolds) that lie outside the field of (hetero)aromatic systems

Marson CM. New and unusual scaffolds in medicinal chemistry. Chem Soc Rev. 2011; 40(11):5514

Set of Shape (helix, beta-sheet, strand, loop) Mimetics

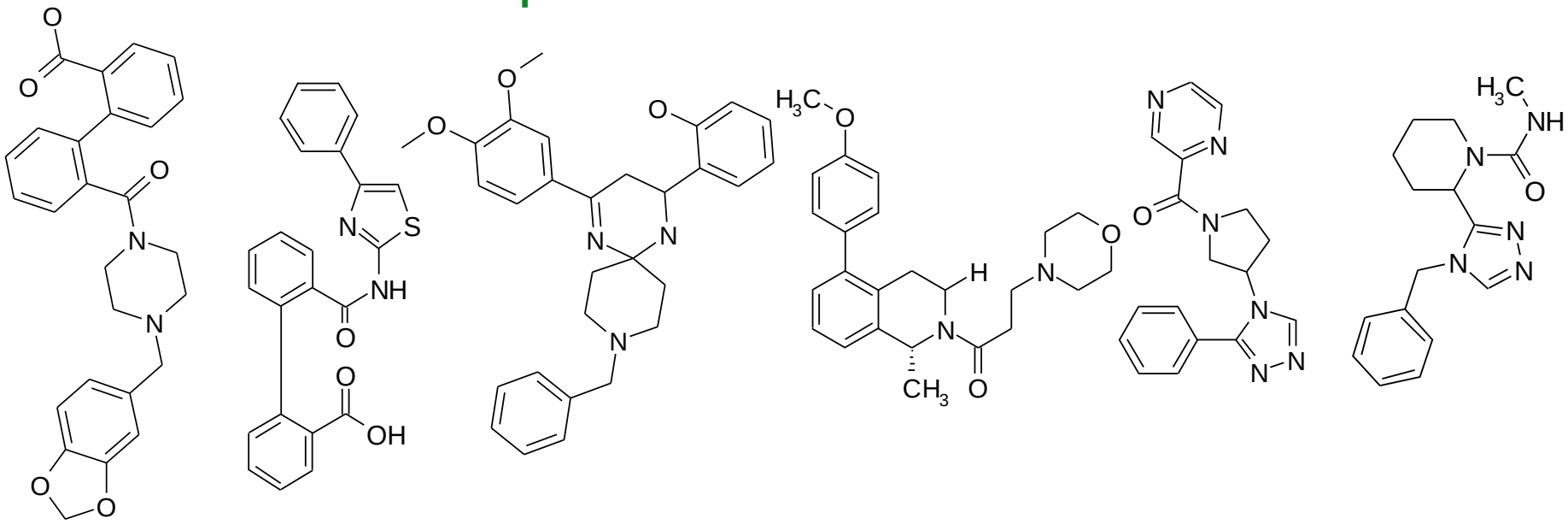
❖The α-helix is the most abundant secondary structural element in proteins and is an important structural domain for mediating protein–protein and protein–nucleic acid interactions



❖Strategies for the rational design and synthesis of α-helix mimetics have not matured as well as other secondary structure mimetics such as strands and turns

❖The design of such agents involves the mimicry of side-chain residues on one face of the alpha-helix; these residues frequently play a key role in mediating

Examples



~ 400 new scaffolds proposed; Library contains 10K Shape-mimetics

Examples of PPI Targeted Chemistry & Libraries (ChemDiv's Experience)

Chemokine pGPCRs: CCR1, CCR2, CCR3, CCR4, CCR5, CCR7, CCR8, CXCR1, CXCR2, CXCR3, CXCR4;

Other pGPCRs: Galanin Gal1, Gal3; Bradykinin B1, B2; Neurotensin NT1, NT2; Orexin OX1, OX2; Opioid-like ORL-1; Tachykinin NK1, NK2, NK3; Bombesin BB1, BB2, BB3; Urotensin UTR2; Protease-activated receptor 1; Glucagon GR; Glucagon-like GLP1; Vasopressin AVPR; etc.

Integrins: alphaIIb/beta3 (Fibrinogen), alphaVbeta3 (Vitronectin), alpha4beta1, etc.

Heat Shock Proteins: HSP70, HSP90

Apoptosis: BCL-2, BCL-w, BCL-xl, MCL-1, IAP1, IAP2, XIAP, caspase-3, etc.

Pathways: Hedgehog Hh, Smo; WNT; WNT – beta-catenin; Notch, etc.

Our Expertise in Non-Peptide Peptidomimetic Library/Compound Design

❖Tsaloev A., Ilyin A., Tkachenko S., Ivachtchenko A., Kravchenko D., Krasavin M. Cyclic products of the Ugi reaction of aldehydo and keto carboxylic acids: chemoselective modification. ***Tetrahedron Letters***. **2011**, ***52***: 1800–1803.

❖Kysil V., Khvat A., Tsirulnikov S., Tkachenko S, Williams C., Churakova M., Ivachtchenko A. General Multicomponent Strategy for the Synthesis of 2-Amino-1,4-diazaheterocycles: Scope, Limitations, and Utility. ***European Journal of Organic Chemistry***. **2010**; 1525–1543.

❖Kysil V.M., Khvat A., Tsirulnikov S., Tkachenko S., Ivachtchenko A. Multicomponent approach to unique 1,4-diazepine-2-amines. ***Tetrahedron Letters***. **2009**; ***50(24)***: 2854-2856.

❖Balakin K.V., Ivanenkov Y.A., Tkachenko S.E., Kiselyov A.S., Ivachtchenko A.V. Regulators of chemokine receptor activity as promising anticancer therapeutics. ***Current Cancer Drug Targets***. **2008**; ***8(4)***: 299-34.

❖Kiselyov A.S., Tkachenko S.E., Balakin K.V., Ivachtchenko A.V. Small-molecule modulators of Hh and Wnt signaling pathways. ***Expert Opinion on Therapeutic Targets***. **2007**; ***11(8)***: 1087-1101.

❖ Savchuk N.P., Tkachenko S.E., Balakin K.V. Design of pGPCR-targeted Libraries. In Rognan D., ed. ***Ligand Design for G Protein-coupled Receptors.*** Methods and Principles in Medicinal Chemistry (Volume 30). Weinheim: Wiley VCH. **2006**, pp. 137-164.

❖ Kysil V., Tkachenko S., Khvat A., Williams C., Tsirulnikov S., Churakova M., Ivachtchenko A. TMSCl-Promoted Isocyanide-Based MCR of Ethylenediamines: an Efficient Assembling of 2-Aminopyrazine Core. ***Tetrahedron Letters***, **2007**; ***48(36)***: 6239-6244.

Thank You!!!